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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1954

ORIGINAL ARTICLES

PLACENTAL TRANSMISSION OF THE LUPUS ERYTHEMATOSUS FACTOR

By Robert G. Bridge, M.D.
RESIDENT

AND

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The incidence of pregnancy during the course of disseminated lupus erythematosus is rather rare even today when there is some evidence that adrenal corticotrophic hormone (ACTH) and cortisone prolong the life of a patient suffering with this disease[5,22]. There is no constant effect of pregnancy on this disease, some reports indicating amelioration of symptoms and others indicating that the disease is made worse[22]. Recently we have had the opportunity to study a patient with disseminated lupus erythematosus who became pregnant and delivered a viable full term baby.

In January, 1948, Hargraves, Richmond, and Morton[9] first described an abnormal cell seen in the bone marrow of patients suffering with disseminated lupus erythematosus. This has since become known as the Hargraves or L E cell. Since that time, this work has been confirmed by Haserick[14] and other investigators[4,16]. Further work[13] has shown that this so-called L E cell is dependent upon an L E factor present in the serum of patients with disseminated lupus erythematosus. It is now known that L E cells can be demonstrated in several ways: 1) In heparinized bone marrow of patients with lupus erythematosus[9,14]. 2) By the use of peripheral blood of patients with lupus erythematosus, either heparinized or oxalated[8,24] blood, or clotted specimens[7], for example the "Two Hour Blood Clot" technique[17]. 3) Normal bone marrow or normal leukocytes of peripheral blood may be incubated with L E plasma[4,11,18] and 4) L E cells may be demonstrated in the skin by inoculation of normal skin with L E plasma[20], or through the production of a cantharides blister in patients with disseminated lupus erythematosus[27].

L E cells are not seen in the direct smear of bone marrow or peripheral blood. In effect then, this cell can be

produced if one has L E serum and leukocytes and allows them to react.

The L E cell is a leukocyte (almost always a neutrophil) which contains a homogeneous reddish-purple staining inclusion body. It has been shown[16] that the inclusion bodies consist chemically of partially depolymerized desoxyribonucleic acid which is derived from nuclear substance of either lymphocytes or neutrophils. This altered nuclear substance is then thought to be phagocytized by normal neutrophils producing the L E cell.

So far we have discussed only the L E cell. Actually, there is produced by the various methods described more than just the L E cell. These additional components are also included under the term L E phenomenon and consist of:

1) The L E rosette, which is a group of neutrophils surrounding a reddish-purple staining mass. 2) The droplet inclusion cell, a neutrophil which usually has an eccentrically placed nucleus and in whose cytoplasm are reddish-purple staining inclusion droplets of varying size and shape. 3) Extracellular reddish-purple staining bodies which are similar to the inclusion bodies, but which are not yet phagocytized. All of these reddish-purple staining masses are thought to represent depolymerized desoxyribonucleic acid. These various parts of the L E phenomenon are thought to be different phases of the same basic mechanism and, in part, steps in the formation of the classical L E cell.

The question arises as to how often this phenomenon occurs in disseminated lupus erythematosus, and how often it is encountered in other diseases or in normal persons. From a review of the literature[3,4,16,21,29] we have found that in approximately 90% of over 200 cases of disseminated lupus erythematosus the L E phenomenon was demonstrable. The phenomenon is nearly always present during the acute phase of the disease but occasionally it has been known to be less positive and rarely even to disappear during the subacute or chronic stage of the disease and in remissions obtained with ACTH and cortisone.

In other collagen and miscellaneous diseases the L E phenomenon was not seen in over 200 reported cases[2,10]. In a review of the literature to date we have been able to find only 11 cases reported positive for L E phenomenon which were thought not to be disseminated lupus erythematosus. These were 3 cases of severe penicillin reaction[26] and one case each of pernicious anemia[4], dermatitis herpetiformis[4], chronic discoid lupus erythematosus[4], miliary tuberculosis[16], hemolytic anemia[16], generalized moniliasis[6], leukemia[25], and multiple myeloma[19]. It is the general feeling that this test is not only very sensitive but also relatively specific for disseminated lupus erythematosus.

There are 2 additional facts known about the L E factor. As has been previously stated, the L E factor is present in the serum of patients with disseminated lupus erythematosus, but more specifically it has been demonstrated by Haserick[13] that this factor is in the gamma globulin fraction of serum. Secondly, this gamma globulin fraction in disseminated lupus erythematosus is capable of producing antibodies (in rabbits) which can precipitate the L E factor[12], while antibodies against normal gamma globulin fail to do so. Thus it is apparent that L E gamma globulin differs immunologically from normal gamma globulin and that it is antigenic.

The purpose of this study was to make observations on 2 previously unreported phases of this L E factor as it concerns the production of the L E

phenomenon. 1. It is known that some antibodies which are found in the gamma globulin cross the placental barrier as witness the fact of transfer of passive immunity to the newborn baby. The question is, does the L E factor which is a gamma globulin cross the placental barrier? 2. It is known that the L E factor, at least in rabbits, is antigenic. If the L E factor does cross the placental barrier, will it stimulate the production of antibodies in the baby?

Material and Methods. The mother was a 20-year-old white housewife who was known to have had disseminated lupus erythematosus since June of 1950. The principal manifestations were weakness, fever, albuminuria, polyarthritis, dermatitis in a butterfly distribution over the face, and Raynaud's phenomenon. The clinical course was typical of the acute phase modified markedly presumably by cortisone therapy. Bone marrow examinations had repeatedly demonstrated the L E phenomenon. Therapy consisted primarily of cortisone in a dosage of 50 to 100 mg. daily for the past 2 years.

The pregnancy was essentially normal and full term. Cortisone was continued throughout its course, and in addition, ACTH was given for 2 weeks before and one week after delivery. Following premature rupture of the membranes, there was a normal low forceps delivery on December 9, 1952. There was no placenta previa or premature separation of the placenta. The placenta was intact and appeared normal on gross and subsequent microscopic examination.

The following laboratory studies were obtained a few hours prior to delivery: The hemoglobin was 13.3 gm. per 100 cc. blood, the erythrocytes numbered 4.92 million per c.mm., and the leukocytes 7,900 with 88% neutrophils, 11% lymphocytes, and 1% monocytes. Urinalysis revealed a trace of albumin but was otherwise negative. The erythrocyte sedimentation rate was 40 mm./hr. (normal 0 to 20 mm./hr.). The hematocrit was 40%. The fasting blood sugar was 81 mg. per 100 cc., the nonprotein nitrogen was 26 mg. per 100 cc., and the serum proteins totalled 6.0 gm. per 100 cc., with 3.8 gm. albumin, and 2.2 gm. globulin. The serum gamma globulin was 1.3 gm. per 100 cc. (normal 0.7 to 1.1). Serum sodium was 133 mEq./L. or 305 mg. per 100 cc., serum potassium was 3.7 mEq./L. or 14.5 mg. per 100 cc., and the serum chlorides (as NaCl) were 598 mg. per 100 cc. (normal 580 to 650). A direct Coombs test was negative. The circulating eosinophils numbered 11 per c. mm. (normal 25 to 400). An electrocardiogram was within normal limits.

TABLE 1.—L. E. PHENOMENON AT DELIVERY

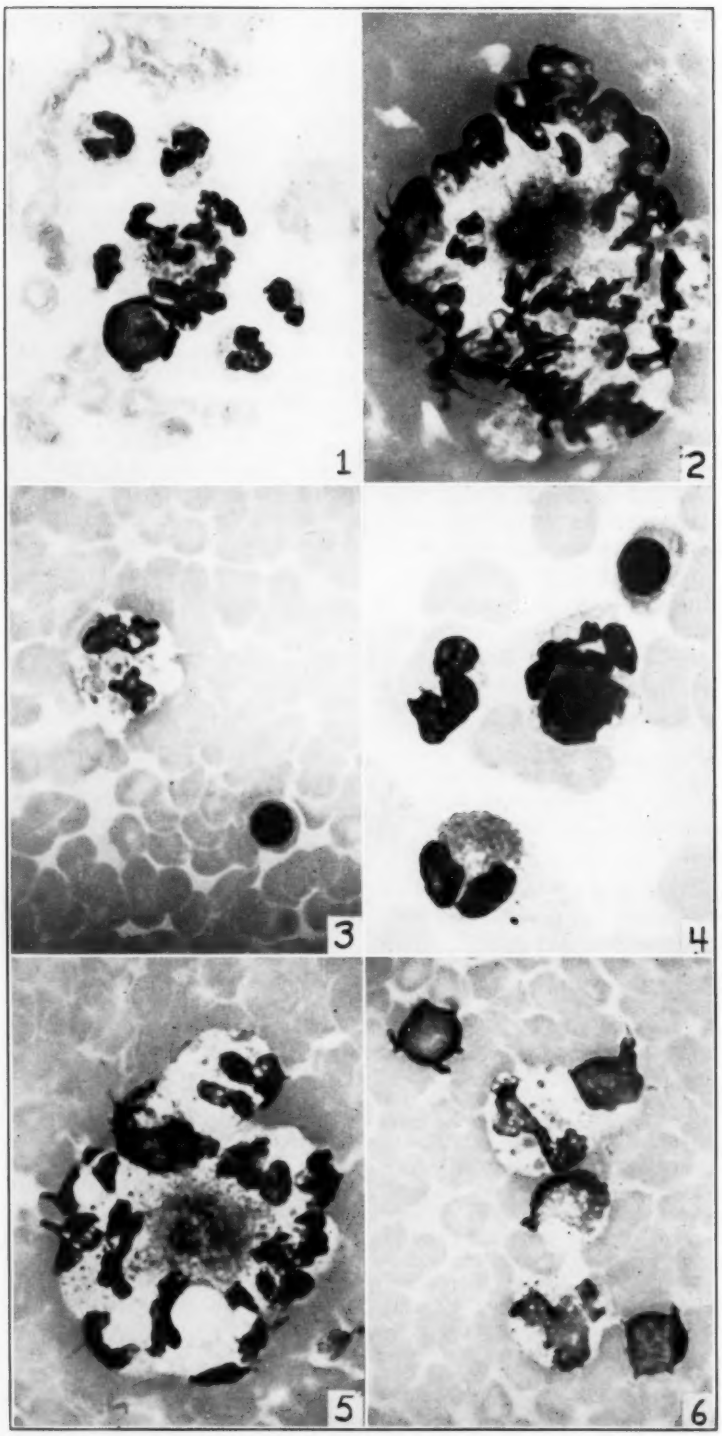
	Mother (venous blood)	*Baby (cord blood)*
Two-hour blood clot technique	Moderate L E phenomenon. Occasional L E cells and rosettes. Frequent droplet inclusion cells.	Mild L E phenomenon. Infrequent L E cells and rosettes. Occasional droplet inclusion cells.
Plasma incubated with normal marrow	Moderate L E phenomenon but less than in blood clot preparation. Infrequent L E cells. Occasional rosettes and droplet inclusion cells.	Very mild L E phenomenon. Rare L E cells. Occasional rosettes. Infrequent droplet inclusion cells.

The postpartum course was uneventful and the patient was discharged home with her baby on December 14, 1952 (5th postpartum day).

The baby was a normal 5 lb. 5 oz. male and has shown normal growth and development during the period of observation. A direct Coombs test on the cord blood was negative.

At the time of delivery, venous blood was collected from the mother and cord blood from the baby. Two-hour blood clot preparations were made from both the mother's venous and the baby's cord bloods. In addition, plasma from these 2 bloods was incubated with normal bone marrow for one hour. Smears were then made from the buffy coat layers and stained with Wright's and Giemsa's stains. These slides were examined microscopically for evidence of the L E phenomenon. A summary of the results may be seen in Table 1.

The slides made from the baby's blood and baby's plasma plus normal bone marrow



Figs. 1 to 6 (Legends on page 5)

showed unequivocal evidence of the L E phenomenon. The unique characteristics of the L E cell leave little possibility of confusion in interpreting the L E preparations.

Figures 1 through 6 are photomicrographs from the L E preparations made from blood collected at delivery. The homogeneity of the L E phenomenon in the mother and baby is evident.

Six hours after birth a tibial bone marrow aspiration was performed on the baby, and a small amount of marrow was obtained. Direct smears and smears of the buffy layer after incubation were stained in the usual manner. Study of the direct smear preparation showed no evidence of the L E phenomenon. This is as would be expected since the L E phenomenon does not appear until the blood is outside the body for several minutes. However, in the slides made from incubated baby's marrow, there was minimal but definite evidence of the L E phenomenon. This was manifested entirely by occasional droplet inclusion cells and infrequent rosettes.

A bone marrow aspiration was also performed on the mother 6 hours after delivery. A small number of L E cells and L E rosettes were seen on smears made from the the buffy layer after incubation of the marrow.

It was believed necessary to examine a normal control group to see whether or not the L E phenomenon could be demonstrated in normal umbilical cord blood. Consequently, cord blood was collected at delivery of 12 presumably normal pregnancies. Blood clot preparations were made in the usual manner. There was no demonstrable L E phenomenon.

The excess plasma collected at delivery was kept frozen. Three and one-half weeks after delivery this plasma was unfrozen and incubated with normal bone marrow. The results were exactly the same as at the time of delivery. The preparation containing the mother's plasma plus normal bone marrow showed a moderate amount of the L E phenomenon, whereas the preparation containing the baby's plasma plus normal bone marrow showed a somewhat lesser amount of the L E phenomenon.

Blood samples were obtained from the mother and baby 7 weeks and 4 months after delivery. The methods of attempting to demonstrate the presence of antibodies were by precipitation and neutralization. On each occasion preparations were made as outlined in Table 2. In the antibody study the plasmas were allowed to stand for one hour prior to mixing with the normal marrow for 2 additional hours. Preparations I, II, and IV were

TABLE 2.—SEVEN WEEKS AND FOUR MONTHS AFTER BIRTH

	Control		*Mother*	*Baby*		*Antibody study*					
	I	*II*	*III*	*IV*	*V*	*A-1*	*A-2*	*B-1*	*B-2*	*C-1*	*C-2*
Mother's plasma		1 0				0 9	0 9	0 5	0 5	0 1	0 1
Baby's plasma				1 0		0 1		0 5		0 9	
Normal plasma	1 0						0 1		0 5		0 9
Normal marrow	0 5	0 5		0 5		0 5	0 5	0 5	0 5	0 5	0 5
Mother's blood			5 0								
Baby's blood					5 0						
Result, 7 wks.	0	+	+	±	±	+	+	+	+	±	0
Result, 4 mos.	0	+	+	0	0	+	+	+	+	±	±

Legends for Figs. 1 to 6

Fig. 1.—L E cell from mother's 2-hour blood clot preparation.

Fig. 2.—Rosette from preparation of mother's plasma incubated with normal marrow.

Fig. 3.—Droplet inclusion cell from preparation of mother's plasma incubated with normal marrow.

Fig. 4.—L E cell from baby's 2-hour blood clot preparation.

Fig. 5.—Rosette from preparation of baby's plasma incubated with normal marrow.

Fig. 6.—Two droplet inclusion cells in a single field from preparation of baby's plasma incubated with normal marrow.

allowed to stand for 2 hours prior to making the smears of the buffy layer. Preparations III and V were by the 2-hour blood clot technique.

At 7 weeks, preparations from the mother (II and III) showed moderate evidence of the L E phenomenon. In preparations from the baby (IV and V) the result was indefinite. Two cells were seen which were slightly suggestive of the L E cell. Also infrequently there was a cell grouping suggesting an L E rosette. Although the evidence is weak, it is slightly suggestive of the presence of the L E phenomenon in the baby's preparations. A statement as to whether it is positive or negative can not be made.

By the technique used there was no evidence of antibodies against the L E factor present in the baby's blood at 7 weeks.

Four months after delivery the mother's blood continued to show the L E phenomenon. However, in the baby's preparations there was no longer even suggestive evidence of the presence of the L E phenomenon.

When mother's and baby's serums were mixed, no precipitation was observed. Neither was there any evidence of antibody presence by neutralization studies at 4 months.

Discussion. We have demonstrated the presence of the L E phenomenon in the blood of the newborn of a patient having disseminated lupus erythematosus. By a suitable control series it was shown that the L E phenomenon is not demonstrable in the normal newborn. Although other remote possibilities might be considered, it seems extremely likely that the demonstration of the L E phenomenon in the baby was dependent upon placental transmission of the L E factor from the mother's serum. The finding of a lesser amount of the L E phenomenon in the baby's L E preparations might be explained on the basis of dilution of the L E factor in the baby's blood. However, the significance of the concentration of the L E factor in relation to quantitation of the L E phenomenon has never been established.

The action of the placental barrier in separating the fetal and maternal circulations in not well understood. From the available information[1,28] it seems likely that the placental membranes act only as an ultrafilter. Therefore, transmission is on a purely physical basis depending on the size of the molecule. However, the possibility of selective placental absorption and secretion has never been conclusively excluded. Because of very marked species variability in placental transmission, results obtained in experimental animals can not be applied to humans. As evidenced by the passive immunity of the newborn, it would seem that at least some gamma globulins must pass the placental barrier. Hypoproteinemia (especially globulin) is present in the normal newborn[1,28]. This might suggest that placental transmission of serum proteins is incomplete; however, the additional factor, that the newborn's ability to produce proteins (especially globulins) is probably inferior, must also be considered. There is little doubt that molecular size is at least one factor determining placental transmission. The very large complex molecules (for example, lipoproteins) do not pass into the fetal circulation. The results of our work therefore suggest that the L E factor probably existed in the maternal circulation as a simple gamma globulin and not combined with any molecule of very large size.

Although disseminated lupus erythematosus has on 4 occasions[21] been reported to occur in members of the same family, it is safe to say that heredity is not considered to be a factor in this disease. Nor do we believe that the presence of the L E phenomenon in the baby described means that the child has now or will develop disseminated lupus erythematosus. It is more likely that the L E factor is a part of the disease process, and that it can be transmitted across the placental bar-

rier without producing the disease in the baby.

The relationship between the L E factor and the disease has never been defined. However, it has been shown by Klemperer[15] that the hematoxylin staining bodies so widely distributed throughout the body in cases of disseminated lupus erythematosus examined at necropsy contain partially depolymerized desoxyribonucleic acid. As previously stated the inclusion body of the L E cell contains the same material. If the L E factor itself is capable of producing any anatomical changes, there was no clinical evidence of any such changes in the baby during our period of observation. However, this possibility was not considered likely and detailed studies to evaluate it were not conducted.

Our inability to demonstrate antibodies to the L E factor in the baby may be explained in several ways. Although such antibodies have been produced in rabbits, it has never been established whether or not the human is capable of producing antibodies to the L E factor. Furthermore, it is well known that antibody production in an infant is inferior to the adult. Our attempt to detect antibodies was by precipitation or neutralization. It is possible that even if antibodies were present they would not be demonstrable by our methods. It is therefore not our desire to suggest that the human is necessarily not capable of antibody production to the L E factor.

It is considered worthy of mention that the so-called "pre L E cell"[23] was seen throughout our work. However, it has been our observation that this cell is seen in many conditions other than disseminated lupus erythematosus. The inclusion of the "pre L E cell" as an important part of the L E phenomenon does not seem warranted at this time, and we did not use it as a criterion for the presence of the L E phenomenon.

Summary. 1. The L E phenomenon has been demonstrated in the newborn of a mother with disseminated lupus erythematosus. Observations on this situation have not been previously reported.

2. The presence of the L E phenomenon in the baby was considered to be a result of placental transmission of the L E factor.

3. Evidence was equivocal but suggestive that the L E phenomenon was still demonstrable in the baby 7 weeks after delivery. It was definitely absent 4 months after delivery.

4. By the methods used there was no evidence of production of antibodies against the L E factor in the baby.

5. The significance of these findings is discussed.

ACKNOWLEDGMENT: We wish to express our appreciation for guidance in this work by Dr. Christopher Parnall, Jr. and Dr. Milton Bohrod.

ADDENDUM: Since this paper was submitted for publication, we have studied another pregnancy in a 26-year-old white housewife with disseminated lupus erythematosus. Evidence of the L E phenomenon was again demonstrable in the umbilical cord blood. Therefore, this second case lends confirmation to our conclusions concerning the placental transmission of the L E factor.

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RELAPSE OF VIVAX MALARIA TREATED WITH PRIMAQUINE AND REPORT OF ONE CASE OF CYANOSIS (METHEMOGLOBINEMIA) DUE TO PRIMAQUINE

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and

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The acute paroxysm of *Plasmodium vivax* malaria can be satisfactorily treated with many drugs, but the prevention of relapses remains a major challenge. The 8-aminoquinolines, especially when potentiated by quinine, have given increasing promise in eradicating the exoerythrocytic phase of the parasite ever since Pamaquine, the most toxic of the group, was first found thus to be efficacious. Recently, primaquine has been reported as virtually non-toxic and practically always effective in preventing relapses. The purpose of this communication is to report 9 cases in which primaquine failed to prevent relapses and one case in which primaquine produced a methemoglobinemic cyanosis in a Caucasian male.

The erythrocytic stage of the malarial parasite has a brief life span and causes the acute symptomatology. The exoerythrocytic or tissue stage is responsible for the reappearance of the parasite in the blood stream months and years after its initial elimination[9]. The cinchona alkaloid, quinine; the acridine, Quinacrine; the 4-aminoquinolines, chloroquine, sontochin, and Camoquine; and the biguanide, Paludrine, all effectively suppress or terminate the acute episode but do not prevent relapse after being discontinued[3]. The relapse rate depends on many factors: natural and acquired immunity, method and intensity of infection, strain of parasite, the drug therapy given, and the period of observation.

James, in 1931[8], demonstrated the efficacy of Pamaquine, an 8-aminoquinoline, as a prophylactic in *Plasmodium vivax* malaria. Though effective against the exoerythrocytic stage of the parasite, the toxicity of Pamaquine at therapeutic levels prevented wide acceptance. In the intensive search for a safer drug many other 8-aminoquinolines including pentaquine and isopentaquine were synthesized. The newest of the group, primaquine, appeared to be effective and less toxic than the other compounds tested[2]. Edgcomb *et al.*[5] inoculated volunteer prisoners with the Chesson strain of *Plasmodium vivax* malaria from infected mosquitoes. Relapse almost invariably followed if the primary attack was treated with quinine, quinacrine, chloroquine, or Paludrine. Treated with primaquine alone (22.5 to 45 mg. of the base daily for 14 days), 5 of 10 subjects had no relapses in the follow-up period of 284 to 333 days. Parasitemia and fever recurred in 12 to 18 days in the remaining 5 cases but were felt to represent a recrudescence, due to incomplete eradication of the trophozoites. The addition of quinine (1,640 mg. of the base daily for 14 days) to primaquine (22.5 to 60

mg. of the base daily for 14 days) resulted in apparent cure in 39 to 40 cases followed 161 to 755 days. Parasitemia and fever reappeared in 4 of 5 cases when the primaquine dosage was reduced to 15 mg. of the base daily for 14 days and the quinine dosage was unchanged. This preliminary report stated that "a daily dose of 22.5 mg. of primaquine base given concurrently with 1,640 mg. of quinine base prevented relapse in practically 100% of cases".

Garrison *et al.*[6] treated 286 patients during an acute episode of *Plasmodium vivax* malaria in Korean veterans with 1,500 mg. of chloroquine base in 72 hours and 15 mg. of primaquine base daily for 14 days. Clinical relapse did not occur in 231 patients followed 4 to 11 months. Of the control group of 232 patients treated with chloroquine alone, 64 (27.6%) relapsed within 4 to 11 months following treatment. They concluded that a combination of primaquine and chloroquine in this dosage prevented relapses in nearly all cases of naturally acquired Korean strain *Plasmodium vivax* malaria.

TABLE 1.—ESSENTIAL DATA IN 9 CASES OF KOREAN P. VIVAX MALARIA RELAPSING AFTER STANDARD SHIPBOARD PRIMAQUINE THERAPY*

Case No. Race-Age	*Dates of Korean service*	*Dates of malarial episodes & treatment given prior to shipboard primaquine therapy**	*Date and duration of shipboard primaquine therapy*	*Relapse dates after shipboard primaquine therapy*	*Date of positive smear*	*Treatment given after shipboard primaquine therapy**
1. W 23	June 51–Mar. 52	—	May 52–10 days	June 52	?	chloroquine 4500
				4 Sept. 52	6 Sept. 52	Camoquine 700
2. W 42	Feb. 51–Feb. 52	—	Mar. 52—14 days	July 52	?	chloroquine 1500
				31 Aug. 52	6 Sept. 52	primaquine 210
3. W 24	Mar. 51–Jan. 52	—	Feb. 52—10 days	Apr. 52	?	chloroquine 4500
				July 52	?	Camoquine 800
				11 Sept. 52	11 Sept. 52	Camoquine 800
4. W 20	May 51–Mar. 52	—	Apr. 52—14 days	20 July 52	20 July 52	primaquine 210
5. W 25	Aug. 51–May 52	—	Aug. 52—12 days	22 Sept. 52	26 Sept. 52	primaquine 210
6. W 22	July 51–Apr. 52	—	Apr. 52—14 days	21 July 52	27 July 52	primaquine 210
7. W 20	Oct. 50–Apr. 52	Oct. 51—chloroquine 4800	May 52—9 days	23 Sept. 52	24 Sept. 52	Camoquine 800 chloroquine 1500
8. W 21	July 51–May 52	—	May 52—14 days	July 52	?	chloroquine 4500
				30 Aug. 52	30 Aug. 52	primaquine 210
9. W 21	May 51–Mar. 52	Sept. 51—chloroquine 1500	Apr. 52—14 days	June 52	?	chloroquine 1500
				July 52	?	chloroquine 1500
				15 Sept. 52	16 Sept. 52	Camoquine 800

* Expressed as mg. base.

Toxic manifestations frequently encountered in therapeutic dosages of the 8-aminoquinolines are methemoglobinemia, vomiting, and abdominal cramps. Severe hemolytic anemia and hemoglobinuria were not observed in 699 white adults receiving 10 to 240 mg. of primaquine base daily[4], although they occurred in Negroes in the dosage of 30 mg. daily for 7 days[7]. The administration to Korean veterans returning via ship to the United States of 15 mg. of primaquine base daily for 14 days was initiated in September, 1951[1], but did not become really effective until later. Methemoglobinemia sufficient to cause cyanosis was not detected in

In 1951, there were 194 cases of *Plasmodium vivax* malaria in the 15,234 admissions to Letterman Army Hospital; in 1952, there were 112 cases in the 12,730 admissions. From July, 1952, to January, 1953, there were 9 patients (Table 1) admitted to this hospital with positive smears, who, on careful questioning, had received and

retained 15 mg. of primaquine base daily prophylactically for 9 to 14 days while returning from Korea during a period when placebos were not being administered. All had received suppressive therapy with 300 mg. of chloroquine base weekly while in Korea. Two had experienced malarial episodes prior to shipboard therapy. Five patients had episodes of fever, presumably due to malaria, subsequent to the primaquine therapy and prior to the present admission. All were in good health otherwise at the time of the present relapses, which were treated with the 4- or 8-aminoquinolines in conventional dosage.

Case Report. A 23-year-old Caucasian soldier was apparently well when he boarded ship in the Far East for transfer to the United States. He received 15 mg. of primaquine base daily from 2 to 15 September, 1952. On 7 September, he experienced nausea, eructations, and vomiting, which gradually subsided. Three days later he noted blurring of vision, a bluish discoloration of his lips and nails, and unusual darkness of his blood when he cut himself shaving. He was hospitalized aboard ship and transferred to this hospital on arrival in the United States because of "unexplained cyanosis".

Physical examination on admission on 17 September revealed an afebrile white male in no acute distress with a grayish hue to the skin and an obvious bluish discoloration of the mouth, tongue, lips, and nail beds. The retinal arteries were a dark purple in color, closely approximating the color of the veins.

The conventional laboratory tests were within normal limits. The methemoglobin level on 20 September was 2.7 gm. per 100 cc.

The patient was given 300 mg. of methylene blue. Twelve hours later there was no discernible blueness of the skin, mucous membranes, or nail beds. Methemoglobin at this time measured 0.58 gm. per 100 cc. The patient was discharged to duty.

Comment. Only a small number of cases of malaria are observed at this hospital due to the fact that comparatively few Korean evacuees are stationed in this immediate area. Many other Korean evacuees have undoubtedly received prophylactic primaquine therapy and relapsed elsewhere.

The administration of 15 mg. of primaquine base daily for 14 days does not always eradicate the late tissue phases of the Korean strain of *Plasmodium vivax* malaria. Although the drug is highly effective in both artificially and naturally acquired infections, this dosage schedule does not completely cure all individuals.

Clinically evident cyanosis due to increased methemoglobinemia may occur with this dosage. Further observations may disclose cases of severe anemia and hemoglobinuria, especially in the darker skinned races. The 8-aminoquinolines are toxic drugs with a low margin of safety when compared with the suppressive antimalarials. We should be aware of their limitations and await the results of further long range studies.

Summary. 1. Nine cases of relapse of Korean strain *Plasmodium vivax* malaria were observed following the prophylactic administration of 15 mg. of primaquine base daily for 9 to 14 days.

2. Methemoglobinemia sufficient to cause cyanosis was observed in a Caucasian male following the prophylactic administration of 15 mg. of primaquine base daily for 14 days.

3. Korean strain *Plasmodium vivax* malaria is not invariably cured and toxic effects are not wholly avoided with the present dosage schedule of primaquine.

ADDENDUM: Four additional cases of Korean strain *Plasmodium vivax* malaria, who had previously received standard primaquine shipboard therapy, have been seen in relapse.

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SPONTANEOUS PNEUMOTHORAX

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It is the purpose of this paper to present the recommended treatment and management of spontaneous pneumothorax together with a statistical evaluation of 60 cases seen at the U. S. Naval Hospital, Philadelphia, Pa. These cases were admitted to the hospital in the 4½ year period between January 1, 1949 to June 1, 1953. The cases were selected only on a basis of availability and completeness of clinical records.

During this period 70 patients were admitted to the medical chest service of this institution with the diagnosis of spontaneous pneumothorax. Because the records of 10 of these patients were incomplete or unavailable they were not included in this study. In the period covered there were 1879 patients admitted to the chest service of which 3.72% were admitted with the diagnosis of spontaneous pneumothorax. These figures were a part of a total hospital admission of 69,415 patients. Spontaneous pneumothorax presented a total incidence of .1008% or approximately one of every 1000 patients admitted to the hospital.

These figures are considerably higher than those of Myerson[12] and the series of Cohen and Kinsman[3]. The reason for this is probably the military nature of this hospital, in which the greater number of patients admitted are within an age group in which spontaneous pneumothorax occurs most frequently. Spontaneous pneumothorax occurs most often between the ages of 20 and 30 years. It occurs most frequently in males, and the majority of patients admitted to this hospital are males. In 1943, there were 873 admissions to all Army hospitals in this country for simple benign idiopathic spontaneous pneumothorax[15].

A literal definition of the term pneumothorax is "air in the chest;" however, for generations the term has indicated the presence of air in the pleural space. Pathologically there are 3 routes by which air may reach the pleural space: 1) through the chest wall itself as in missile wounds of the thorax, 2) through the pulmonary tree and lung itself by rupture of the visceral pleura, and, 3) rarely when air dissects its way along the peribronchial interstitial tissue and then ruptures into the pleural space at the junction of the visceral and parietal pleura.

The second factor is the most common cause and is the one with which this paper is mainly concerned. Subpleural blebs have long been accepted as the common site of the air leak, and as long ago as 1915, Hagashi and Fischer[5] reported the microscopic finding of scar formation around a bronchiole acting as a check valve to produce inflation of such pleural blebs. Other causes, such as bronchospasm, mucosal edema and infection, may likewise produce respiratory obstruction and peripheral over-inflation of a bleb with subsequent rupture. These

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Fig. 1 Fig. 2

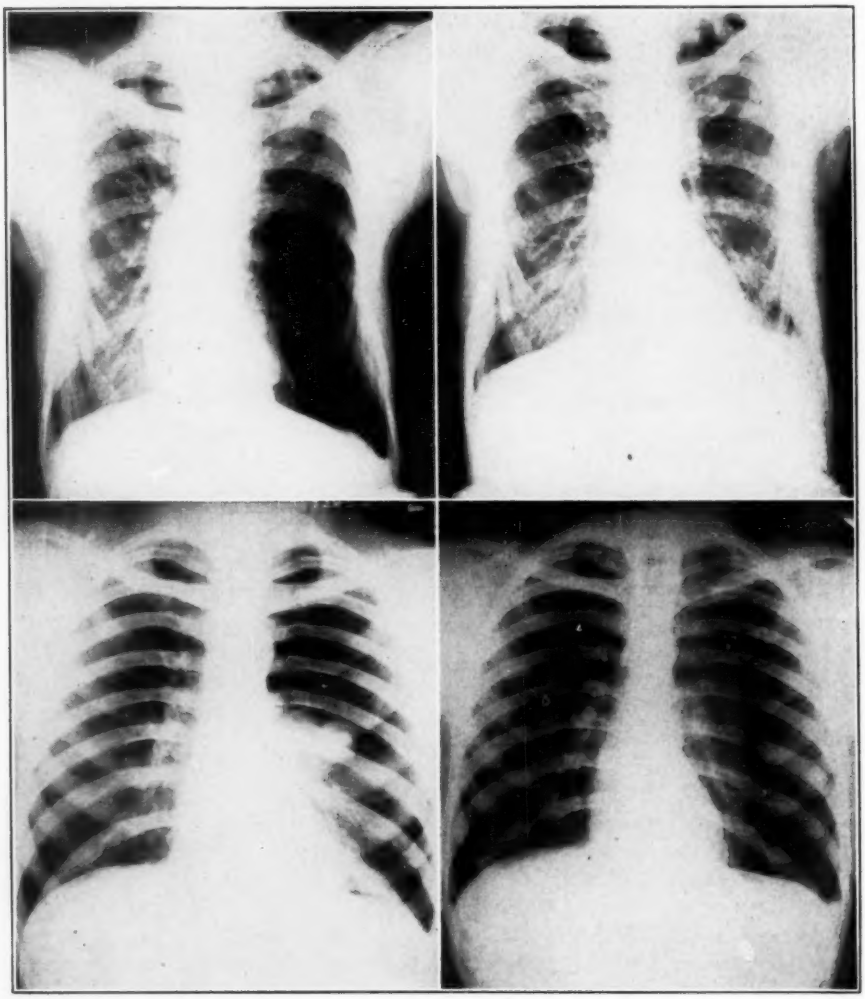

Fig. 3 Fig. 4

Fig. 1.—A posterior-anterior chest roentgenogram to illustrate the increased blood volume in the right lung field simulating infiltrative lesions.

Fig. 2.—The same case as shown in Fig. 1. after re-expansion of the left lung has occurred showing the disappearance of the densities.

Fig. 3.—A posterior-anterior view of the chest of a patient with a left-sided pneumothorax illustrating how the overlapping collapsed lung tissue may simulate pulmonary infiltration.

Fig. 4.—The same chest roentgentographic view as in Fig. 3. after re-expansion has occurred. One notes the absence of any parenchymal disease.

blebs may be congenital in origin, but the disease rarely has familial antecedence[3]. They may be due to the forcing of air into the upper lobes during severe exercise. This occurs in competitive sports which may account for the increased frequency in young adult males.

There are many who still believe that the most important lung condition causing spontaneous rupture of the visceral pleura is tuberculosis. In our cases and in cases reported in other studies tuberculosis has been ruled out as a common cause of the condition. Perry[16] in a review of the literature could find only 6 of 250 cases who developed tuberculosis. Of his own 85 patients, none had tuberculosis. Only one of Kjaergaard's 49 patients was found to have tuberculosis[8].

Of our 60 cases only one was proven to have tuberculosis. Twenty-one (or 35%) had a negative reaction to the tuberculin skin test, (purified Protein Derivative), 30% had incomplete records in this respect, and 35% had a positive skin test. Only the one patient was found to have sputum and gastric washings positive on culture for *Mycobacterium tuberculosis*. Sedimentation rates were normal in the remaining 59. Roentgen-ray and fluoroscopic examinations were uniformly negative in these 59 patients. The congestion of the opposite lung from increased relative blood volume, which is always present to some degree, should not be mistaken for tuberculous infiltration[16]. Likewise the overlapping of the collapsed lung sometimes resembles exudates. (See Figs. 1, 2, 3 and 4.)

While rupture of emphysematous blebs is probably the most common cause of the condition, it must not be forgotten that tuberculosis and other diseases do occasionally present themselves as simple spontaneous pneumothorax. New growth of the lung and pleura are etiologic agents. Xanthomatosis and lymphoblastoma have been known to cause the condition. We have noted also a relationship between certain blood dyscrasias and spontaneous pneumothorax[10]. In this report we are concerned only with pneumothorax developing in apparently healthy individuals in the absence of other disease.

Air in the pleural space causes an interesting and characteristic physical diagnostic picture. The chest on the affected side moves less with respiration. The interspaces are not as prominent and often the supraclavicular space is obliterated by the increased intrapleural pressure. Thus it is possible to make the diagnosis by careful inspection of the patient.

The mediastinal structures may move causing a shift of the trachea, apex beat, and percussion outline of the heart. Auscultation reveals absent or diminished breath sounds on the affected side, and occasionally these will sound amphoric, especially if the patient breathes forcibly. There is no other disease that will give amphoric breath sounds all over the hemothorax. Another physical diagnostic sign of value is the well known coin test. Also, if the patient is made to cough while the examiner is listening over the collapsed portion of the lung a peculiar "konk" will be heard. This is not present on the normal side. We have found this a particularly valuable sign in discovering small pneumothoraces.

One must remember that large cysts of the lung may mimic air in the pleural space.

The ages of the patients studied ranged between 17 and 71 years. Two-thirds of the cases occurred between the ages of 20 and 29 years. (See Table 1.)

Of the 60 cases 5 were Negro males. There was only one woman in the whole group. The condition is infrequent among women.

TABLE 1.–NUMBER OF CASES OCCURRING IN EACH AGE GROUP

15 to 19 years	5 cases
20 to 24 years	18 cases
25 to 29 years	23 cases
30 to 34 years	6 cases
35 to 39 years	1 case
40 to 44 years	2 cases
45 to 49 years	0 case
50 to 54 years	1 case
55 to 59 years	3 cases
Over 60 years	1 case
Total	60 cases

The character of onset in the 60 cases was remarkably similar. In 83% of the cases the initial complaint was chest pain on the affected side, usually described as sharp. Four patients said the pain radiated to the shoulder, one to the elbow, and one said the pain radiated down the left arm to his little finger. One must guard against confusing the pain of coronary artery disease and that of spontaneous pneumothorax. There was one of this group which was wrongly diagnosed by the admitting physician as having a coronary occlusion. Three of the patients complained of pain in the abdomen. In one case this was diagnosed on admission as appendicitis. Fortunately he was not operated on. The referred abdominal pain may, as in this instance, be confused with intraperitoneal disease. One patient complained of pain in the left chest which radiated to the left ear. This is a referred pathway to the nerve of Arnold.

Over half (53%) of the patients were dyspneic from the onset or by the time of admission to the hospital. The average elapsed time between initiation of complaints and admission to the hospital was 5 days.

Of the 60 cases only 8 patients were engaged in any sort of strenuous physical exercise. Two were playing football, one was engaged in gymnastics, one was swabbing a deck, two were painting, and one received a sharp blow to the chest. The other was at work inside a refrigerator. Eleven patients were either asleep or just arising in the morning when the attack occurred. "Perhaps deeper respiration after a period of shallow respiration, as in sleep, may produce the rupture of the pleura"[16].

There appears to be no relationship between strenuous physical activity and the onset of the episode. Table 2 lists the type of physical activity which the patients included in this report were doing at the time of onset.

TABLE 2.–TYPE OF PHYSICAL ACTIVITY AT TIME OF ONSET

Strenuous exercise	8 patients	13.3%
Normal activity	40 patients	66.6%
Asleep or just awakening	11 patients	18.3%
Discovered on routine Roentgen-ray	1 patient	1.6%

The right and left lung were affected with almost the same frequency in this series of cases. There were 30 cases in which collapse occurred on the left side and 29 cases in which the pneumothorax occurred on the right side. One case had a 25% collapse of each lung. This was the only bilateral pneumothorax of the group. The percentage of collapse varied from a minimal 5% to a total 100%. There was one case of tension pneumothorax. The data is illustrated in Table 3.

The diagnosis was confirmed in all patients by Roentgen-ray and fluoroscopy. Full expiration will aid in the demonstration of small pneumothoraces on both the fluoroscopic and roentgenographic examinations.

No correlation between the amount of collapse and the severity of symp-

toms could be established. Some patients with total collapse of one lung had no dyspnea while others who had only a minimal pneumothorax were short of breath. The severity of the pain did not indicate the size of the pneumothorax.

TABLE 3.—NUMBER OF CASES AND THE DEGREE OF COLLAPSE

25% or less	24 cases
26% to 50%	13 cases
51% to 75%	5 cases
76% to 100%	18 cases
Total	61 cases (One case of bilateral pneumothorax)

The principle of treatment in spontaneous pneumothorax is to attain re-expansion by closure of the ruptured pleural bleb. The majority of patients will satisfactorily seal the rupture and re-expand their lung within a few days to a few weeks by conservative management, that is, by bed rest alone. With this type of patient nothing else need be done. If dyspnea is uncomfortable oxygen by nasal catheter or mask may be employed for the short interval it is needed, and if pain or cough is distressing sedation and analgesics may be used for their control.

The patient is fluoroscoped daily to observe the progress of his re-expansion. If a positive tuberculin skin test is obtained, at least one gastric lavage concentrate is cultured for *Mycobacterium tuberculosis*. Of course, if an infiltrative lesion is noted more complete studies are done. Usually with this management the patient exhibits progressive re-expansion of his lung. But if the patient does not show any change in the amount of his collapse within 5 to 7 days, then water-sealed negative drainage should be instituted. Occasionally we may delay a few days longer. Experience has shown us that if expansion is not occurring by this period, the chances of complications, such as marked pleural fluid formation, empyema, and non-expandable lung are greatly increased. It is our practice to introduce a soft rubber catheter into the pleural space and connect this to a water-sealed drainage bottle, with the tube from the patient adjusted so as to be no more than one to 5 cm. beneath the water level. This bottle is then connected to a Stedman suction pump through a "safety valve" bottle setup so as to adjust the negative pressure between 10 to 15 cm. of water. (See Fig. 5.) As a rule the second or third anterior interspace is used and the procedure is done at the patient's bed. The pump must always keep ahead of the air leak. Pressure adjustments may be made depending upon the re-expansion rate and the amount of air being sucked out. Occasionally 2 catheters with pumps must be employed. Antibiotics are administered during the time the catheter is being used.

In most cases this is our only indication for the catheter treatment. However, certain clinical problems dictate its use from the outset: 1) tension pneumothorax, 2) a physiologically impaired contralateral lung, and, 3) associated cardiac disease with marked dyspnea. This type of treatment usually re-expands the lung within 24 to 48 hours. If the lung does not re-expand by these means, we use about one week as the limit of trial and then advise thoracotomy without further delay.

We do not advise this type of suction drainage in every case of simple pneumothorax as it is being advocated in some clinics today[6]. The reasons we do not believe it is necessary are: 1) the great majority of patients do well with conservative management alone, 2) the introduction of the catheter

is often associated with a slight temperature rise, and, 3) the patient with a catheter requires more care and attention than one without. We do believe, however, that when the indications are present it should be readily instituted. The surprising constancy with which blebs stay healed once expansion has occurred is the crucial fact which allows this type of treatment its success. This plan of management has been instituted in this hospital in the past year. Although the figures are difficult to analyze because of the peculiarities of hospital stay in a military institution, we feel that with our plan of therapy there are fewer complications and a quicker return to duty. Twenty-five per cent of our cases with our indications required intercostal catheter suction for re-expansion. Table 4 lists the number of patients undergoing each type of treatment.

TABLE 4.—METHOD OF TREATMENT EMPLOYED

Treatment	*No. of Patients*
Bed rest alone	43
Aspiration of air with bed rest	8*
Catheter suction drainage	6
Resection of blebs	1
50% glucose	1
Talc insufflation	1

*Before institution of regimen as outlined in this report.

One of the cases was a 71-year-old man in whom the insertion of 2 catheters with attached Stedman pumps failed to re-expand the lung. At thoracotomy three large blebs were resected and the lung re-expanded uneventfully. (See Figs. 5 & 6.)

Eight of the patients (13%) presented the problem of recurrent pneumothorax. One of these was treated with 50% glucose intrapleurally and another with talcum powder poudrage to produce an aseptic pleuritis. Neither of these cases after a year's follow-up has suffered any further recurrence.

We do not feel that aspiration of the air by thoracentesis with maintenance of negative pressure by water trap is a valid procedure. In those cases where it is necessary to remove the air artificially the intercostal catheter and Stedman pump are superior.

One factor which should not be overlooked in the treatment of pneumothorax is the danger of transporting such patients by aircraft. Most common carriers and military transports are not equipped with pressurized cabins and oxygen. This form of transportation is potentially dangerous for patients at high altitudes with air in the pleural space. The trapped air expands and may jeopardize pulmonary function, and in turn life.

The most common complication seen was the accumulation of fluid on the side of the pneumothorax. Nearly all of these resorbed, and in only one case was it necessary to aspirate the hydrothorax.

One patient had bilateral pneumothorax. He was a 26-year-old white male who noticed the sudden onset of substernal pain while talking. On admission to the hospital 5 days later he was found to have a 25% collapse of both lungs. He was asymptomatic and was treated conservatively. Both lungs re-expanded in 14 days. This man had a recurrence of the pneumothorax on the left 2 years later which was treated in the same manner with a prompt and satisfactory re-expansion.

One patient was extremely dyspneic, cyanotic, and uncomfortable and was found to have a tension pneumothorax. The increased pressure was released by needle aspiration with immediate relief of the patient. He also made an uneventful recovery. In the present management routine we would have treated this patient with catheter suction drainage.

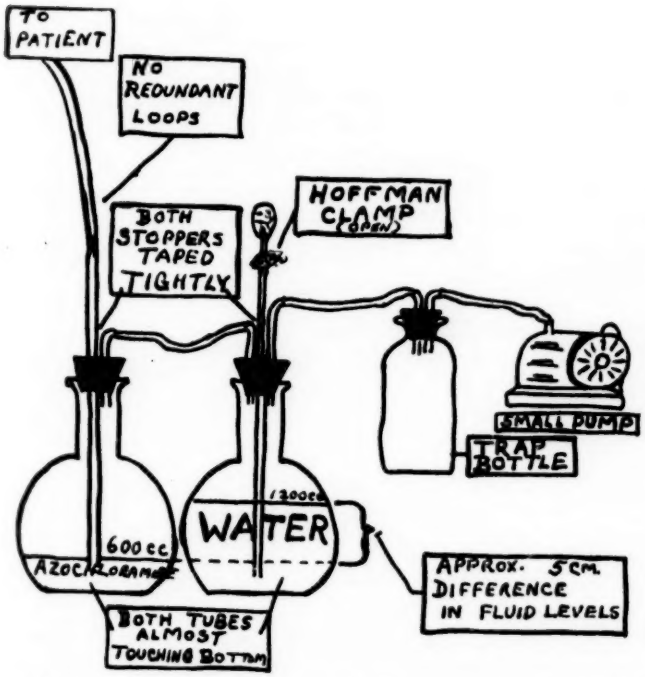

Fig. 5.—This is a diagrammatic sketch of the bottle and pump setup employed when catheter negative suction drainage is instituted.

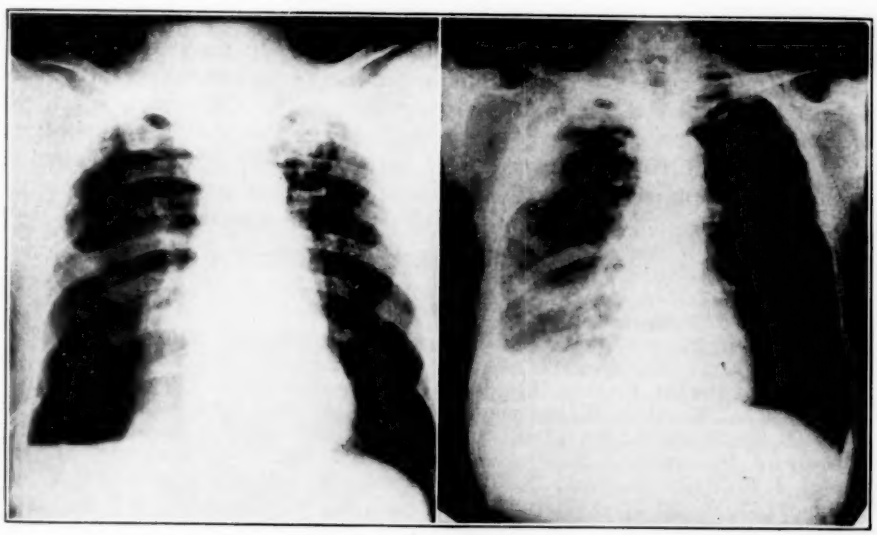

Fig. 6 Fig. 7

Fig. 6.—This illustrates the extent of the right-sided pneumothorax in this case which did not re-expand even after a second catheter was placed within the pleural space.
Fig. 7.—This is an early postoperative film showing full expansion of the right lung after three large emphysematous blebs were resected.

The prognosis of spontaneous pneumothorax is nearly always excellent. There were no deaths in this series and a very low morbidity. The complications of the disease which may threaten life are 5: 1) tension pneumothorax, 2) hemopneumothorax with continued severe bleeding, 3) bilateral pneumothorax, 4) unexpandable lung, and 5) empyema. The air is usually quickly resorbed as has been the experience with therapeutic pneumothorax. The disease does recur with annoying frequency. Thirteen and three-tenths per cent of cases in this series had a recurrence. In other series the incidence of recurrences has been reported as between 4.7 and 21%[7,12,14,17].

Summary and Conclusions. 1) About one in every 1000 patients admitted to the Philadelphia Naval Hospital has a spontaneous pneumothorax. Because of its frequency in young adult males military and civilian physicians should be familiar with all phases of the disease.

2) In this series of 60 patients only one was found to have tuberculosis. Thirty-five per cent of these showed a negative reaction to the tuberculin skin test. It is believed that tuberculosis is not an important cause of this disease. The most common cause is probably the rupture of subpleural blebs and bullae.

3) The physical activity of the patient at the time of onset bears no relationship to the attack. Nor do the symptoms have any relationship to the amount of collapse present.

TABLE 5.—NUMBER OF COMPLICATIONS ENCOUNTERED IN SERIES

Complications	*Number of Patients*	*Per Cent*
None	35	58.3
*1 Hydrothorax	11	18.3
Recurrent pneumothorax	8	13.3
Tuberculosis	1	1.6
Pneumococcal pneumonia	1	1.6
Congestive heart failure	1	1.6
*2 Failure to expand	1	1.6
Bilateral pneumothorax	1	1.6
Tension pneumothorax	1	1.6

*1 This cannot be considered an actual complication since usually it is minimal and resorbs promptly.

*2 This case required resection of emphysematous blebs before expansion could be obtained.

4) A routine of preferred therapy is described. The majority of patients will respond satisfactorily to conservative management. In those cases with the prescribed indications, intrapleural catheter suction drainage is considered the superior method of treatment.

5) The most common complication seen was hydrothorax, and usually this absorbed spontaneously.

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RE-EVALUATION OF THE ETIOLOGY OF POSTARSPHENAMINE JAUNDICE

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INSTRUCTOR IN MEDICINE

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During the years when treatment of syphilis consisted of numerous injections of heavy metal compounds, jaundice was seen quite frequently in syphilis treatment centers. Because of the known toxicity of arsenic and because of the apparent time relationship between the onset of therapy and the appearance of jaundice, the condition was generally attributed to arsenic sensitivity[12].

As early as 1920, however, an infectious etiology was suggested[13] and during the next 20 years many attempts were made to explain such peculiarities as the occurrence of "early" and "late" types of jaundice, the tendency of cases to come in groups resembling epidemics, and the vague, but unmistakable, time relationship between epidemics of catarrhal jaundice in the general population and cases of postarsphenamine jaundice in the syphilis clinic population[11-14]. However, it was not until homologous serum hepatitis was described[4-6] that a plausible explanation for some of the peculiarities of postarsphenamine jaundice became apparent. Since that time, it has been generally accepted that at least some of the cases of jaundice which were seen in these clinics were actually cases of homologous serum hepatitis which had been transmitted by contaminated syringe or needle[1-3,8].

The study reported in this paper was undertaken in an attempt to evaluate the concept that postarsphenamine jaundice represents homologous serum hepatitis and to clarify the role of arsenic-containing compounds in the causation of hepatitis.

Material and Methods. The material for this study was obtained from records of patients treated in the syphilis clinic of Vanderbilt University Hospital. Prior to the advent of penicillin and rapid therapy, this clinic was very active. Forty-seven cases of jaundice were seen during the years when arsenic-containing compounds were being used. These cases are listed in Table 1. Since jaundice was felt to represent a serious manifestation of drug sensitivity, it was watched for very carefully and it is doubtful that any clinical case went unrecognized or unrecorded.

Unusually accurate and easily verified records kept in the syphilis clinic made it possible to determine the exact dates of all visits, medication, venipunctures, and jaundice. This information was placed on a composite chart which clarified the relationships between all of these patients. Figure 1 shows a small portion of this composite data sheet. Horizontal lines represent the course of a given patient. Vertical arrows represent possible contacts between patients. Each block represents a clinic visit. The upper 8 patients had jaundice prior to January 10, 1933, when Fig. 1 begins. Numbers 16 and 17 had jaundice during the period covered by the illustration. Number 18 developed jaundice later in 1933.

To illustrate how case contacts could be extracted from the data sheet, it can be seen that patient number 17 received arsphenamine and bismuth on March 14 but could not have been exposed then because none of the previously jaundiced patients visited the clinic on that day. On January 20, January 27, February 3, and February 17, however, he could have been exposed to several different previously jaundiced patients. Since these possible donor patients received only

bismuth, this means of transfer must be considered.

After completion of the composite data sheet, material was organized in various ways to study the importance of various factors. First of all, cases of early and late post-arsphenamine jaundice were identified. Secondly, the 2 groups were characterized and a continuous pattern of possible exposure demonstrated in the late type of jaundice. The third portion of the study was then undertaken to demonstrate by statistical means that cases in the late group were probably homologous serum hepatitis. The methods used and the findings of these studies are discussed below.

Results. PART 1. The first portion of this study compares the date of onset of jaundice with the start of arsenic therapy. Forty-four of the 47 patients are included in this breakdown. These cases are listed in Table 2, Groups 3 and 4. The other 3 patients must be

TABLE 1.—PATIENTS WHO DEVELOPED JAUNDICE WHILE ATTENDING THE VANDERBILT MEDICAL LUES CLINIC BETWEEN JANUARY 1928 AND JANUARY 1943

Patient	*Initials*	*Sex*	*Date of Jaundice*
1.	B. L.	F	February 1928
2.	Wm. R.	M	January 1929
3.	L. S.	F	July 1929
4.	R. W.	F	February 1930
5.	V. J.	F	March 1930
6.	C. C.	F	March 1930
7.	J. B.	M	July 1930
8.	J. H.	M	September 1930
9.	G. P.	M	September 1930
10.	S. J.	M	October 1930
11.	H. H.	F	January 1931
12.	A. C.	M	October 1931
13.	W. L.	M	September 1932
14.	J. H.	M	October 1932
15.	B. M.	F	November 1932
16.	S. C.	F	April 1933
17.	B. A.	M	May 1933
18.	M. P.	F	August 1933
19.	I. N.	F	September 1934
20.	B. D.	F	March 1935
21.	M. S.	F	March 1935
22.	D. S.	M	April 1935
23.	E. H.	F	June 1935
24.	E. C.	F	September 1935
25.	W. A.	M	December 1935
26.	M. R.	F	April 1936
27.	R. M.	M	July 1936
28.	J. B.	F	September 1936
29.	J. W.	M	September 1936
30.	N. G.	F	October 1936
31.	J. B.	M	November 1936
32.	B. S.	F	May 1937
33.	G. B.	M	May 1937
34.	M. R.	M	October 1937
35.	J. B.	F	November 1937
36.	M. D.	F	March 1938
37.	L. F.	M	April 1938
38.	M. C.	F	April 1938
39.	T. B.	M	October 1938
40.	J. H.	F	April 1939
41.	M. H.	F	July 1939
42.	M. P.	F	July 1939
43.	W. K.	M	August 1939
44.	E. H.	F	August 1939
45.	L. Y.	F	September 1939
46.	V. B.	F	January 1940
47.	R. W.	M	April 1940

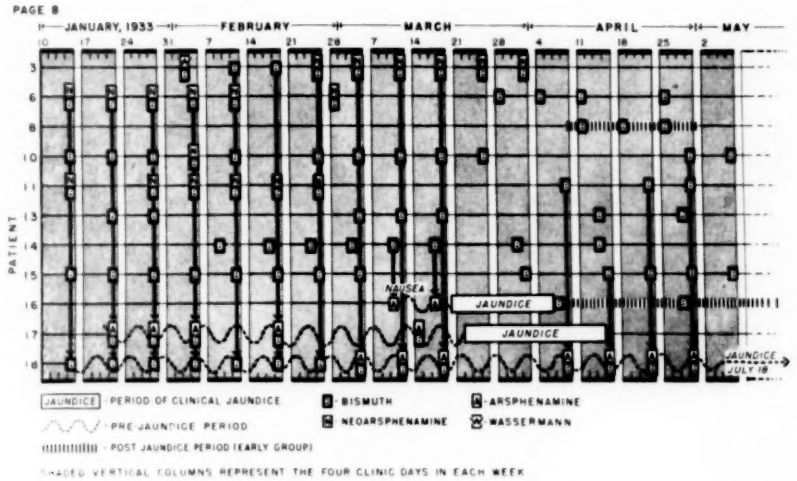

Fig. 1.—Portion of Composite Data Sheet.

TABLE 2.—GROUPING OF PATIENTS BY POSSIBLE INCUBATION PERIODS (SEE TEXT)

Patient	*Weeks Between Admission and Jaundice*	*Number of Possible Exposures*
Group One		
1.	Unknown	Unknown
Group Two		
10.	Unknown	Unknown
36.	Unknown	Unknown
Group Three		
25.	1	0
16.	2	0
21.	2	0
47.	2	0
8.	2	0
24.	3	2
35.	3	3
37.	3	1
44.	3	2
46.	3	0
19.	3	0
22.	4	0
7.	5	1
27.	6	0
2.	7	1
Group Four		
38.	11	8
40.	13	1
41.	15	5
20.	15	11
13.	15	6
45.	17	16
12.	18	5
31.	19	7
39.	19	4
17.	20	8
30.	21	9
34.	23	2
11.	24	9
5.	25	8
18.	26	18
23.	29	6
6.	30	12
15.	34	25
3.	34	9
4.	35	18
42.	35	3
29.	38	0 (25)*
26.	44	6
43.	46	11
9.	48	2
33.	65	36
28.	77	0 (8)**
32.	90	39
14.	125	0***

* No known exposures to patients in the late group; 25 exposures to patients in the early group.
** No known exposures to patients in the late group; 8 exposures to patients in the early group.
*** No demonstrated exposures to any patient who had had jaundice previously. (See text.)

excluded because the exposure history of each patient is incomplete. One patient (B.L.) had jaundice prior to the establishment of an adequate record system. The other 2 patients (Group 2) received treatment part of the time in another hospital and exact records of these treatments are not available.

The classical division of the charted patients into early and late forms is rather striking (Fig. 2). A group of 14 cases appears within 3 weeks of the start of treatment with a peak in the third week. A larger group of 29 cases appears much later in the course of treatment and is spread over many months with no sharp peak. The average incubation period in the early group is shorter than that classically assigned to homologous serum hepatitis. Whether this indicates that the 2 groups represent separate diseases or 2 types of the same disease is difficult to determine. Certainly there were definite clinical differences between the 2 groups as indicated by Table 3, but there is also evidence that patients in the early group had a form of communicable jaundice. This will be discussed in detail subsequently.

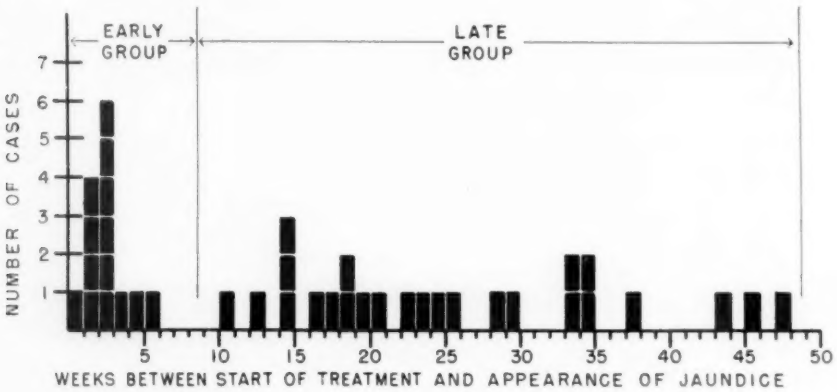

Fig. 2.—Relationship of Start of Arsenic Therapy to Onset of Jaundice.

TABLE 3.—DIFFERENCES BETWEEN EARLY AND LATE TYPES OF JAUNDICE

Characteristic	*Early Type*	*Late Type*
Incubation period	Less than 25 days	11 to 40 weeks
Skin reactions	Common	Absent
Nausea and vomiting	Common	Rare
Possible exposure to serum of cases with jaundice in the past	Occasional	Practically universal

PART 2. The second portion of the study deals with the late group (Group 4) of 29 patients who were exposed to hypodermic needles 11 weeks or more prior to the onset of their jaundice. By analysis of the composite data sheet, every possible contact with previously jaundiced patients in this clinic who had had jaundice in the past was determined. A diagram of the overall exposure pattern among members of this group is shown in Fig. 3. It is apparent that there were essentially 2 separate series of cases. The first began in 1929 when patient No. 3 developed jaundice, possibly due to

transfer of infection from patient No. 1. Subsequently, a number of cases appeared, the last 2 coming in the first months of 1935. Although the exact pattern of disease transfer is unknown, the most frequent pathways of exposure are indicated by solid black lines. Other exposures are dotted.

In 1935, a second series of cases began to appear. A theoretical transfer of infection from patients Nos. 3 and 9

Patient No. 14 was the only member of this group of 29 patients in whom no possible contact was demonstrated. Exclusion of cases Nos. 28 and 29 leaves 26 patients who had exposures to one or more patients who had had the late type of jaundice in the past. This suggests that some or all of these patients could have had homologous serum hepatitis.

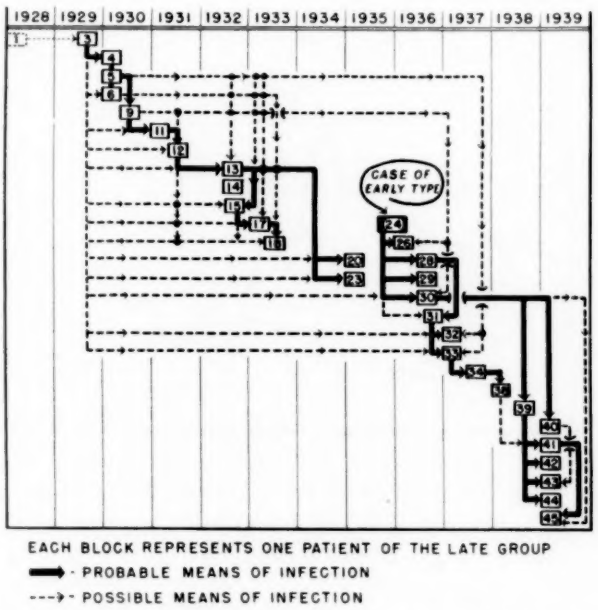

Fig. 3.—Possible Pattern of Virus Transfer Among Patients in the Late Group.

of the first series can be demonstrated to several of the patients in this group. Patients Nos. 28 and 29, however, were exposed only to patient No. 24 who had the early type of postarsphenamine jaundice. This raises the important question of whether or not the early types of postarsphenamine jaundice were some sort of viral hepatitis and if so, whether such cases might give rise to an epidemic of homologous serum hepatitis. This problem will be discussed subsequently.

PART 3. The third portion of this study is an attempt to show by statistical means that the group of late postarsphenamine patients probably had homologous serum hepatitis. All 29 patients are used in this analysis since exclusion of the 3 patients described above would introduce a factor of selection which might invalidate the results.

There are several ways in which this material might be organized. The simplest way to plot the exposures is

to include every possible exposure of each patient to cases who had had the late type of jaundice previously. This would include all significant exposures as well as all exposures which did not involve the transfer of virus. A statistically significant peak of exposure 70 to 140 days prior to the onset of jaundice would be evidence that the exposures were important in the causation of the jaundice. Figure 4 demonstrates such an organization of the data and a peak is seen to occur. The height of the peak is not significant, however, and the reason is obvious. A patient may have been exposed 10 or 20 times but only one exposure was needed to transfer the virus and all other possible contacts merely made it impossible to know when the transfer occurred. Furthermore, the wide variation in the incubation period of homologous serum hepatitis spreads the significant exposures out over several weeks so that the overlap on non-important exposures makes analysis very difficult.

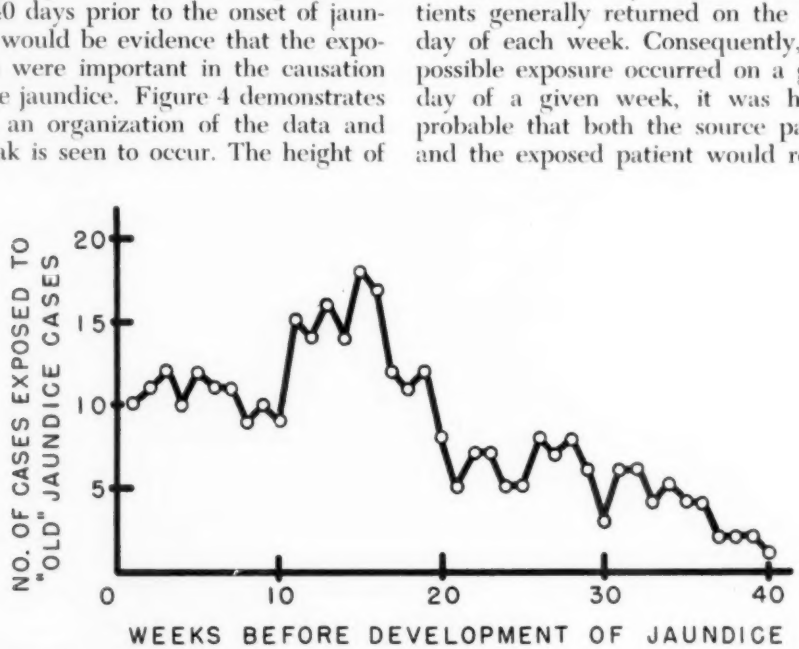

Fig. 4.—Relationship of Number of Possible Exposures to Length of Time Prior to the Onset of Jaundice.

The problem then becomes one of multiple possible exposures in most patients with only one exposure being significant insofar as transfer of virus is concerned. The reason for this large number of possible exposures is easy to determine. Patients made weekly visits to the clinic and, although the clinic met on 4 days of the week, patients generally returned on the same day of each week. Consequently, if a possible exposure occurred on a given day of a given week, it was highly probable that both the source patient and the exposed patient would return on the same day of the next and subsequent weeks. It becomes apparent that a method of analysis must be used which takes this multiple exposure into account and yet gives full weight to a single exposure.

Close examination of Fig. 1 reveals a characteristic of the clinic which provides the basis for the next portion of the study. In any given week, there were days when patients who had had jaundice in the past came to the clinic and days when they did not. Occasionally every one of the 4 clinic days in a given week had such a patient, but

as a rule there were only one or two such days per week. Furthermore, this distribution of patients would continue unchanged for months at a time.

The corollary to this situation is the fact that a new patient coming into the clinic might or might not come in on the same day as a patient who had had jaundice in the past. The probability of starting treatment on such a day would be directly proportional to the number of these days in the week. If we designate as "J-days" those days on which patients who had had jaundice in the past visited the clinic, we can indicate this probability by the formula:

$$P = J/C$$

Where P = probability of coming into the clinic on a "J-day"

J = number of "J-days" in a week

C = number of clinic days in the week (always 4 in this study).

This calculation can be further extended to determine the probability of exposure during the entire period prior to the onset of jaundice. In most cases the distribution of "J-days" remained the same during this period (Fig. 5). In these cases the total probability was equal to the probability for a given week. When this was not the situation the number of "J-days" for the entire period could be determined by assuming that one "J-day" in any given week in the period makes that day a "J-day" for every other week in the period (Fig. 6).

Another factor to be taken into account in determining the probability of exposure of a given patient to an individual who had had jaundice in the past is a change in the day the new patient visited the clinic. Normally, patients kept certain days for their visits in each week. When this was not the case, however, the patient's probability of exposure was considerably increased. This new probability by the formula:

$$P = 1 - \frac{C(n-r)!}{C(n\ !\ r)}$$

Where P = probability
C = constant
n = number of possibilities (in this case 4)
r = number of trials

using this formula, we get the probabilities listed in Table 4.

WEEKS

CLINIC DAY	1	2	3	4	5	6	7	8	9	10	TOTAL
1											
2	J	J	J	J	J	J	J	J	J	J	J
3											
4											
TOTAL	1	1	1	1	1	1	1	1	1	1	1

CALCULATION OF PROBABILITY: $P = \frac{J}{C} = \frac{1}{4}$

Fig. 5.—Method of Determining Total Probability When Pattern of "J-days" Does Not Vary from Week to Week.

The application of this method of determining the probability that each individual patient would visit the clinic on a "J-day" yields the probabilities listed in Table 5. From these individual probabilities, a total probability can be obtained which will indicate the likelihood that 26 of 29 patients visited the clinic on "J-days" by chance alone. The method of testing most applicable to this situation is the Poisson series of trials. This method is independent of those patients who had a probability of 1 and of those who had a probability of 0. The calculations outlined in Table 6 indicate that the high incidence of "J-day" visits among the patients under consideration did not occur by chance alone, but that the visits on these days had a definite relationship to the subsequent development of jaundice.

Discussion. This study demonstrates a consistent exposure pattern among patients who had late postarsphenamine jaundice. Two to 5 months prior to the development of jaundice a significant number of these patients received parenteral medication on the same day as a patient who had had the late type of postarsphenamine jaundice previously. This would indi-

WEEKS

CLINIC DAY	1	2	3	4	5	6	7	8	9	10	TOTAL
1						J	J	J			J
2	J	J	J	J	J	J	J	J	J	J	J
3											
4			J								J
TOTAL	1	1	2	1	1	2	2	2	1	1	3

CALCULATION OF PROBABILITY: $P = \frac{J}{C} = \frac{3}{4}$

Fig. 6.—Method of Determining Total Probability When Pattern of "J-days" Varies from Week to Week.

TABLE 4.—DETERMINATION OF PROBABILITIES FOR VARIOUS "J-DAY" AND "PATIENT-DAY" COMBINATIONS (SEE TEXT)

No. "J Days" per Week	*No. Patient Days per Week (trials)*	*Probability of visiting Clinic on "J Day"*
1	1	$\frac{1}{1}$
1	2	$\frac{1}{2}$
1	3	$\frac{1}{3}$
1	4	$\frac{1}{4}$
2	1	$\frac{1}{1}$
2	2	$\frac{2}{2}$
2	3	$\frac{2}{3}$
3	1	$\frac{1}{1}$
3	2	$\frac{2}{2}$
4	1	$\frac{1}{1}$

cate that this exposure was significant and would in turn suggest that these patients actually had homologous serum hepatitis.

The mechanism by which transfer of virus occurred is not clear but at least some of the transfers seem to have occurred by means of bismuth needles. Three patients in the late group developed jaundice before they had received a single injection of any arsenical preparation. In the past such cases have been labeled "post-bismuth jaundice"[10], but it seems likely that all cases of jaundice of this delayed type were in reality homologous serum hepatitis. This possibility was first suggested 14 years ago by Lane[8].

Analysis of the early group of post-arsphenamine jaundice cases in this study indicates a number of very interesting facts. The sharp peak of cases within 3 weeks after the start of arsenic therapy is strong evidence that arsenic-containing compounds were in some way related to the de-

TABLE 5.—DETERMINATION OF INDIVIDUAL PROBABILITIES

Patient	*"J Days" per Week*	*"V Days" per Week*	*Probability of "J" Contact*
Group Three			
25	0	1	0
16	2	1	1/2
21	1	1	1/4
47	0	1	0
8	1	1	1/4
24	2	1	1/2
35	3	1	3/4
37	2	1	1/2
44	3	1	3/4
46	0	1	0
19	2	1	1/2
22	1	1	1/4
7	1	1	1/4
27	0	1	0
2	1	1	1/4
Group Four			
38	2	2	3/4
40	2	2	3/4
41	2	2	3/4
20	1	1	1/4
13	2	1	1/2
45	3	3	1
12	1	3	3/4
31	2	2	3/4
39	2	1	1/2
17	2	1	1/2
30	2	1	1/2
34	3	2	1
11	2	1	1/2
5	1	1	1/4
18	3	1	3/4
23	1	2	3/4
6	1	1	1/4
15	2	1	1/2
3	1	1	1/4
4	1	1	1/4
42	3	2	3/4
29	2	1	1/2
26	2	1	1/2
43	3	2	1
9	1	1	1/4
33	4	2	1
28	2	2	3/4
32	4	1	1
14	1	1	1/4

TABLE 6.—STATISTICAL TESTING OF DATA

Probability	*No. of Cases*	*No. Expected on "J-day"*	*No. Observed on "J-day"*
1	5	5	5
5/6	7	5.83	6
3/4	1	0.75	1
1/2	9	4.5	8
1/4	7	1.75	6
Totals	29	17.83	26

Total No. cases expected to occur on "J-day" is 17.83 ± 2.155.

$$\frac{\text{Observed No.} - \text{Expected No.}}{\text{Standard deviation}} = \frac{8.1667}{2.155} = 3.79$$

P = 0.001

velopment of liver damage. Certainly these cases fail to conform to our present-day concept of homologous serum hepatitis in that, in the majority of cases, no parenteral injection or blood sampling occurred long enough before the onset of jaundice to allow for an adequate incubation period. On the other hand, some of the cases in the early group did have some demonstrable exposure to previous cases of jaundice a short period of time before the development of jaundice and the possibility that they might have had an accelerated type of serum hepatitis must be borne in mind. Such accelerated types of serum hepatitis have been postulated previously[3,8,9].

The possibility exists that arsenotherapy increases the susceptibility of humans to infection by the virus of infectious hepatitis or serum hepatitis. Such a concept could explain the early onset of jaundice and yet the apparent transfer of virus from such a patient to a subsequent patient who then developed jaundice after an incubation period compatible with serum hepatitis.

Another factor to be taken into consideration in evaluating the early group is that these patients may merely represent examples of previously unrecognized infectious hepatitis which is discovered upon the first or second doctor visit, and thus bears no relationship to the start of arsenic therapy but instead to the start of patient-doctor relationship. Such a concept could not explain, however, those cases who received preliminary bismuth therapy and then developed jaundice immediately after the start of arsenic therapy.

An interesting incidental observation made in this study is that fear of injection of arsenic-containing compounds into patients who had had postarsphenamine jaundice previously appeared not to be justified. Several patients received arsenic-containing compounds at some time subsequent to their period of jaundice and in no case was recurrent jaundice or other ill-effect demonstrated. Examples of this can be noted in Fig. 1. This situation had been observed by workers in the field of syphilis therapy[7] but prior to the understanding of homologous serum hepatitis, no adequate explanation was forthcoming. It is interesting to note, however, that during the later years of arseno-therapy at the Vanderbilt syphilis clinic, arsenic-containing compounds were used with increasing regularity in such patients after their jaundice had cleared clinically.

Some of the patients in the early group and the one patient in the late group who had no demonstrable exposure probably had infectious hepatitis. Certainly, in a clinic such as this, sporadic instances of infectious hepatitis are to be expected and such cases would be included in a group of patients gathered as were these.

Summary. 1. Cases of postarsphenamine jaundice occurring in a syphilis treatment center are reviewed.

2. The early and late occurrence of postarsphenamine jaundice is demonstrated.

3. Evidence is presented indicating that cases of the late type were probably homologous serum hepatitis.

4. Possible relationships of arsenicals, infection and patient-doctor contact to the cases of early postarsphenamine jaundice are discussed.

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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: REPORT OF A CASE WITH RARE HEMOGLOBINURIA TREATED WITH CORTICOTROPIN

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hemolytic disease differing from the other acquired hemolytic anemias in that the defect resides in the cells, which are peculiarly susceptible to hemolysis with slight decrease in the pH of the plasma. Although prior to 1937 apparently only 38 cases had been described, Crosby, in 1951, reviewed 123[3]. The clinical entity also is known as the Marchiafava-Michelli syndrome, Marchiafava having termed the disease chronic hemolytic anemia with perpetual hemosiderinuria in 1928[6,20]. The designation Paroxysmal Nocturnal Hemoglobinuria essentially is a misnomer since the constant feature of the disease is hemosiderinuria rather than hemoglobinuria[20,28].

The hemolysis is produced by a normal thermolabile plasma component[7,13] similar to, if not identical with accelerator globulin[1,4], which causes hemolysis of PNH cells, but not of normal cells. The increased nocturnal hemolysis, as evidenced by increased hemoglobinuria in the morning urine, is due presumably to diminished pulmonary ventilation during sleep with consequent retention of carbon dioxide and decreased pH of the blood[12]. The ingestion of moderate quantities of an acid salt (NH_4Cl) for brief periods of 2 or 3 days also induces minor hemolytic crises.

The hemolytic mechanism in PNH is intravascular, in contrast to the congenital hemolytic anemias, in which there is an acceleration of the normal reticulo-endothelial ("extravascular") degradation of hemoglobin; consequently, the serum bilirubin and the fecal and urinary urobilinogen are not greatly elevated. Since the erythrocytes lose their hemoglobin directly into the circulating plasma, the kidney assumes the major role in excretion of the pigment. Some of the iron derived from the hemoglobin is lodged as hemosiderin in the renal epithelium, and hemosiderinuria results[5]. The degree of hemoglobinemia varies with the rate of hemolysis; hemoglobinuria occurs only when the hemoglobin exceeds the renal threshold (30 mg. per 100 cc.)[25]. Infrequently the rate of hemolysis may be so slow that the plasma hemoglobin rarely, if ever, exceeds the renal threshold; in such instances hemoglobinuria is rarely, if ever, noted. Several such cases have been described[14,18,21]; thus, hemoglobinuria is not a necessary feature of the disease[14].

Presumptive tests in the diagnosis are a strongly positive Prussian-blue reaction for hemosiderinuria (trace amounts are occasionally observed in other acquired hemolytic anemias)[28], and Hegglin's heat resistance test[15]. Ham's test for acid hemolysis[13] is diagnostic, providing hemolytic anemia caused by hemolysins is excluded[9]. A correlation exists between the hemolytic susceptibility of the erythrocytes *in vitro* and the clinical severity of the disease, the hemolytic susceptibility increasing as the serum is further acidified[19]. The Crosby modification of the Ham test is based on the ability of thrombin to activate the hemolytic factor (accelerator globin) and is specific for PNH.

The disease occurs most frequently in the third decade of life. It is characterized by a macrocytic or normocytic anemia and leukopenia, with a normoblastic hyperplasia of the bone marrow. The clinical manifestations include severe abdominal pain and fever caused by multiple venous thromboses[10,21,24] of minor and major degree, constituting the chief cause of death[4,10,23], and found in all cases studied at necropsy[10,21,24].

Almost all known patients with the disease have died from thromboses, anemia, or infection because no treatment has been found consistently effective. According to Singer spontaneous remissions may occur, thus accounting for the recovery of a few patients who have undergone splenectomy[26]. Large doses of alkali apparently have produced temporary remissions followed by very severe exacerbations[16,19]. Liver and iron were of no benefit. Hoffman and Kracke administered a variety of sympathicolytic and parasympathicolytic drugs; daily subcutaneous injections of pilocarpine apparently afforded temporary relief in one case but other patients were not benefited. Repeated transfusions of washed red blood cells have been of value in decreasing the rate of hemolysis[8,11]; however, hemolysis recurs on cessation of transfusion therapy. Since anticoagulant in sufficient concentration inhibits hemolysis *in vitro*[4,7,14], Dicumarol theoretically should be of value; however, the pronounced difficulty in maintaining sustained prothrombin levels seems to predispose to acute exacerbations. In one recent report a 5-week remission was noted during Dicumarol therapy[17] in a patient in whom dramatic temporary improvement (deceleration of the hemolytic process) had occurred during one of 3 courses of therapy with ACTH. Letman reports no beneficial effect in one patient treated briefly with ACTH[18].

The purpose of this report is to describe a case notable for the rare presence of the manifestation, hemoglobinuria, and also to relate the results of the prolonged administration of corticotropin.

Case Report. The patient, a 26-year-old white female secretary (unit No. 525231) was in good health until the spring of 1950, when she began to experience recurrent attacks of severe abdominal pain of several days' duration, gradually increasing in frequency until they occurred approximately every 2 weeks, and mounting in severity so that relief was obtained only by the use of Demerol. Diet, sedatives, antispasmodics, and injections of liver extract were given with little or no effect.

The patient was first seen by one of us on April 25, 1951. She was treated in the outpatient department as a psychosomatic problem. The attacks of abdominal pain recurred at frequent intervals, finally necessitating admission to the hospital on January 9, 1952, after 4 days of severe pain. The past personal history, family history, and the review of systems were negative. The physical examination was negative in all respects. The pain disappeared shortly after admission to the hospital. Hematologic investigation revealed anemia, probably hemolytic; the erythrocyte fragility and Coombs' tests were

normal. Smears of the bone marrow disclosed an erythroblastic marrow with an increase in stored iron. Gastrointestinal roentgenograms and intravenous pyelograms were negative. The patient subsequently was observed in the outpatient department, but she continued to experience attacks of abdominal pain, and an intermittent backache.

On May 9, 1952, the patient again was hospitalized for 8 days with severe abdominal pain not relieved by codeine, and accompanied by malaise, fatigue, anorexia, nausea, and low grade fever. No change was noted in the color of her urine at this time nor had it been discerned in the past. Laboratory data included a hemoglobin of 8.5 gm. per 100 cc., 3 million erythrocytes, 3360 white blood cells with a normal differential, 3.1% reticulocytes and 190,000 platelets per c. mm. The urinalysis indicated a 1 + reduction, numerous granular casts, and several leukocytes and rare erythrocytes. The serum bilirubin was 0.3 mg. per 100 cc. direct and 1.1 mg. indirect; the fecal urobilinogen was 149 mg. per 24 hours; the urinary urobilinogen was 3.5 mg. per 24 hours. Two urine examinations for hemoglobin were negative, as were the Donath-Landsteiner procedure and tests for heat and cold agglutinins. The Coombs' test and determinations of erythrocyte fragility were normal. The marrow again manifested erythroblastic hyperplasia with increased storage of iron.

At this point a presumptive clinical diagnosis of Marchiafava-Michelli syndrome was made on the basis of severe recurrent abdominal pain accompanied by the following hematologic picture: normocytic anemia with reticulocytosis, leukopenia, and the above marrow findings suggestive of hemolysis, with only borderline elevation of the serum bilirubin and fecal and urinary urobilinogen.

Appropriate laboratory studies were then instituted. The urine was tested for hemosiderin with the Prussian-blue reaction and yielded the 3 to 4 + positive response characteristic of the disease. The Hegglin heat resistance tests and carbon dioxide acidification tests resulted in hemolysis of the patient's erythrocytes but not of normal controls. The Ham test for acid hemolysis, as well as the Crosby modification, also produced marked hemolysis of the cells without hemolysis of normal controls. In accord with the suggestion of Merliss[21], 2 gm. of aspirin were given to the patient at bedtime in an attempt to produce increased hemolysis by minimal acidification of the blood; increased hemosiderinuria was noted in the morning urine. The diagnosis thus was considered as established.

On June 18, 1952, the patient again was hospitalized because of severe abdominal pain, nausea and vomiting; 20 mg. of ACTH* were administered intravenously, with rapid improvement, subsidence of pain and return of the temperature to normal by the following morning. The same medication was repeated for 2 successive days. The patient then received 80 units of ACTH gel (Wilson) intramuscularly and was discharged to the outpatient department where she was given 40 units daily from June 24 to August 1, 1952, when the dosage was reduced to 40 units every other day. On August 11, an episode of moderately severe pain with emesis caused a day's absence from work. The dosage of ACTH gel then was restored to 40 units daily (Fig. 1). The hemoglobin and the erythrocyte values which had risen to 10 gm. and 3.62 million, respectively, during the 7-weeks' remission, decreased to 8.5 gm. and 3.36 million with 11.1% reticulocytes following the attack; the hemosiderinuria and the Ham tests remained positive.

Between August 11, 1952, and September 18, 1952, the patient remained symptom free on the ACTH regimen of 40 units daily with a gradual rise in hemoglobin to 11.5 gm. per 100 cc. (3.88 million red cells with 4.5% reticulocytes). On September 18, 1952, she complained of drowsiness, dizziness, poor coordination and malaise. The serum electrolytes were as follows: potassium 3.2 mEq., chlorides 100.8 mEq., CO_2 33.5 mM per liter, and pH 7.48. The symptoms were attributed to a mild imbalance of electrolytes; the usual daily dose of ACTH was omitted; 2 gm. of potassium chloride were administered orally. That night the patient twice voided wine-colored urine followed by urination every half hour with a resultant loss of 5 pounds in weight during the night. There was very little abdominal pain. The urine contained hemoglobin without red cells and gave the usual positive hemosiderin reaction. The blood picture disclosed evidence of hemolysis in that the hemoglobin of 11.5 gm. on the morning of September 18, 1952, decreased to 10.4 during the next 10 days, with an accompanying drop in the erythrocyte count

*The corticotropin was obtained in generous quantities through the courtesy of Dr. David Klein, The Wilson Laboratories, Chicago, Ill.

from 3.88 to 3.40 million cells per c. mm. The patient was hospitalized for observation for 2 days; her symptoms gradually disappeared during the following week.

The daily administration of 40 units of ACTH gel was resumed September 19, 1952, and continued to December 17, when the patient omitted medication for 2 days because of severe unexplained pain in the left eye. Aspirin, codeine, and Demerol gave relief. ACTH was resumed on December 19, but dark urine was noted on December 19, 20, 21, and 22; there was no recurrence of abdominal pain. Because of the absence of abdominal pain in the 48 hours without ACTH, the dose was reduced to 40 units every other day, beginning December 19, 1952. The patient experienced a slight attack of pain on December 31 and January 1, 1953; she took an extra injection of ACTH and then resumed the schedule, maintaining it without a recurrence of symptoms until March 3, 1953. The hemoglobin became stabilized at 11.0 to 12.3 gm. with an erythrocyte count varying between 3.60 and 4.08 million. The reticulocyte count ranged from 2.5 to 5.2% and the leukocyte count from 5800 to 7850 per c. mm. Despite the clinical improvement, the hemosiderinuria and acid hemolysis tests remained persistently positive.

On March 3, 1953, the quantity of ACTH was reduced to 40 units every third day because of acne and hirsutism. On March 18, 1953, the patient experienced sudden severe unexplained pain in the right costovertebral angle and over the crest of the ilium; Demerol was required for relief. The ACTH was reduced from 40 units every third day to 40 every fourth day, but the abdominal pain recurred after only one such period. The hemoglobin decreased to 10 gm. (11.3 g[illegible] one week prior to the attack) and the erythrocyte count to 3.13 million cells per c. mm. However, the pain rapidly subsided after the administration of 40 units of ACTH for 2 consecutive days. The blood count on March 25, 1953, revealed a rise in the hemoglobin to 10.8 gm. and in the red cell count to 3.29 million per c. mm. (2.6% reticulocytes). With maintenance of the regimen of 40 units of ACTH every third day, the erythrocyte count had, by April 8, 1953, risen to 4.12 million cells per c. mm., with a hemoglobin of 12.5 gm.

The patient remained well on this schedule until the evening of April 17, when she developed an attack of severe abdominal pain, requiring Demerol for relief and persisting until April 23. Red urine was noted in specimens voided on April 21, 22, and 23. Hemosi-

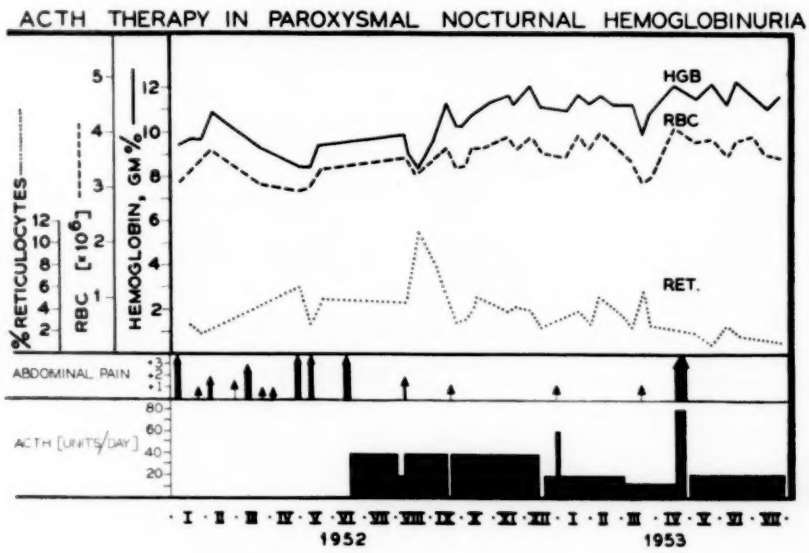

Fig. 1.

derinuria was found in the 2 samples examined. The patient received 40 units of ACTH gel on April 18, none on April 19, 20 and 21; on April 22, 23 and 24, she was given 80 units daily. The pain began to subside on the morning of April 22, and was completely gone by the following day. On April 26, the patient began a program of 40 units of ACTH every other day which she continued until August 7, 1953. It is noteworthy that during this period the rounding of the face gradually decreased. Transitory recurrences of the abdominal pain were noted, none of them even temporarily incapacitating. On August 2, 1953, the aching discomfort in the right costovertebral angle recurred, increasing in severity and requiring Demerol and codeine for relief. On August 6, the abdominal pain returned. On August 7, the patient received 1 cc. (80 units) of ACTH gel rather than the usual dose of 40 units. Urinalysis the next day disclosed the presence of many erythrocytes and only a few leukocytes; the pain had decreased greatly. On August 9, the pain was gone, but the patient was advised to take 80 units of ACTH. She resumed the 40 unit schedule on August 11. Urinalyses on August 12, disclosed a very occasional red cell per high power field and on August 19, a moderate number of erythrocytes; there were no symptoms. The leukocyte count was 6,000 cells per c. mm.; the erythrocyte count 3,720,000 per c. mm.; the hemoglobin 11.3 gm. per 100 cc. and the reticulocyte count 2.0%.

At the present time (November 1, 1953) the patient considers herself in very good health. She is working regularly, and maintaining her usual activities. The experience of the past year seems to indicate that ACTH gel profoundly modifies the symptoms and the blood picture. The facial acne has decreased; there is none elsewhere on the body. The enlargement of the face is moderate, decreasing and not objectionable. More than average facial hirsutism existed prior to therapy and has increased; some girls certainly would object but the patient has not appeared concerned about it. She emphasizes the effect of corticotropin on her emotional status; she is less shy, less inhibited, more talkative, more daring, and so forth. While it is true that ACTH has not controlled entirely the clinical manifestations of the disease, our experience seems to indicate that the symptoms would be controlled by larger doses of the hormone. The limiting factor is our reluctance to increase the medication to the point of disturbing side-effects; hence we attempt to walk the tight rope between underdosage with minimal symptoms and overdosage with Cushing's syndrome.

Discussion. This case illustrates several interesting facts with regard to the clinical features of the disease.

First, the symptoms primarily were those of severe abdominal pain rather than of anemia, fatigue, weakness, pallor, and so forth; the patient was studied and treated for 2 years before the correct diagnosis was made. Snell[27] has pointed out that the disease may simulate primary biliary or hepato-splenic disease; errors in diagnosis may easily lead to surgical intervention with a prohibitive mortality in the cases thus far reported[10]. Thromboembolic lesions and central zonal necrosis of the liver are common findings at necropsy.

Secondly, the patient had a moderate leukopenia. Letman's case[18] had a severe pancytopenia; he suggests that many cases of aplastic or "refractory" anemia are actually atypical forms of PNH, undiscovered because of the absence of hemoglobinuria, now known not to be essential for the diagnosis. In our patient a history of hemoglobinuria was not definitely established except for one episode, recalled after the diagnosis was made. Hemoglobinuria was not noted in the 10 months on ACTH therapy except during the one episode of nocturnal diuresis following temporary withdrawal of corticotropin and the administration of potassium chloride and during the 2 episodes in the period of 6 weeks during which the frequency of ACTH therapy was reduced to every third day.

Thirdly, the degree of hemosiderinuria increased considerably following the administration of 2 gm. of aspirin. The patient states that the only time she had noted dark urine previously was on a morning after the ingestion of codeine and aspirin several months prior to the first hospitalization. Al-

though most authorities state that a pH below 6.9 to 7.22[4] is necessary for hemolysis, Merliss[21] reports that very slight acidification of the plasma is sufficient to increase hemolysis, as successfully demonstrated in his 2 patients by 4 gm. of aspirin administered just prior to bedtime.

Fourthly, the patient remained essentially free of abdominal symptoms for 6 months on ACTH therapy whereas prior to this therapy symptoms had recurred every 2 to 3 weeks. The attacks developing subsequently were milder than the previous episodes. This improvement seems to indicate that the theoretical objection to the use of ACTH on the basis that it predisposes to intravascular thrombosis may not be of too great significance and that corticotropin may be of value in preventing acute exacerbations of both the chronic hemolytic process and the concomitant thrombotic manifestations. The side effects and the problems of long-continued ACTH therapy are, of course, limiting factors.

Summary. 1. A proven case of paroxysmal nocturnal hemoglobinuria with rare hemoglobinuria is described.

2. Corticotropin (ACTH) apparently caused a remission of symptoms of at least 6-months' duration, prevented a recurrence of the acute hemolytic exacerbations, and resulted in sustained rises in the hemoglobin, erythrocyte, and leukocyte levels.

Conclusions. 1. The importance of crises of abdominal pain as the chief presenting symptom of paroxysmal nocturnal hemoglobinuria is emphasized.

2. It is suggested that the disease may be far more common than is usually supposed. Attention should be directed particularly to diagnoses of "surgical abdomen" or atypical "refractory" anemia.

3. While ACTH certainly was of clinical value in the case reported, the wisdom and feasibility of its long-continued use may be questioned. Furthermore, the effect of the hormone on the underlying hemolytic process remains undetermined. The observations are reported in the hope that they may stimulate further investigation of the problem and ultimately clarify the basic mechanisms of the disease.

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FUNDAMENTAL PROBLEMS IN JET INJECTION

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Recent reports cite the results of jet injection for subcutaneous administration of certain drugs as a substitute for the conventional form of hypodermic injection by needle[1-6]. However, the relative tissue damage caused by these two methods of injection remains one of the fundamental problems. A careful study of pathological changes following jet as compared to needle injection has not been reported. Furthermore, since administration of fluids by jet syringe results in a diffusion pattern different from that of needle injection, studies of comparative absorption rates are also desirable.

The principle of jet injection was conceived by an engineer who had observed a relatively painless penetration of the skin by diesel oil particles escaping under high pressure from leaks in conduits. In the past few years several firms have developed instruments capable of needleless jet injection. The "jet syringes" vary somewhat in construction detail but the underlying principle of fluid penetration of the skin under high pressure is common to all devices. Pressure developed within the instruments has been stated to be in the range of 2,300 to 3,900 lbs. per square inch. Injection orifices vary from .003 to .010 of an inch in diameter. As the syringe is discharged, liquid contained in an ampule in the bore of the syringe is forced out of the orifice and through the skin under high pressure. Syringes have been built which accommodate rubber, glass, or inert metal ampules. Hingson has reported that the syringe used in his studies developed a pressure within the instrument of 3,900 lbs. per square inch and projected a jet of liquid through a .003 inch orifice at a speed of 600 miles per hour[3].

Methods. The jet syringes used in this study* have not yet been released for clinical trial. All animals used were rabbits of approximately 2 kg. in weight.

Absorption rates following jet and needle injection were compared in 5 animals by following serial clotting times at 20-minute intervals after the injection of aqueous heparin. Clotting times were performed according to a carefully standardized modification of the Lee-White method; one observer performed all of the determinations in order to lessen errors dependent on variations in technique. Doses of heparin of progressively increasing magnitude were used, and serial determinations were obtained until the clotting time approached that of the pre-injection control.

*Becton, Dickinson & Co., Rutherford, N. J., kindly supplied several experimental models of the Velodermic syringe for this investigation.

Hair was shaved from both ears and the paraspinal areas of all rabbits used for pathological study. Multiple points for injection were carefully marked with India ink to facilitate later identification of the injection site. One cubic centimeter of saline solution colored with a fixed amount of methylene blue dye was used as the injected solution in all cases; the blue color aided somewhat in localization of the area and depth of injection when specimens were taken for histological study.

One rabbit was given multiple needle injections at successive intervals and was sacri-

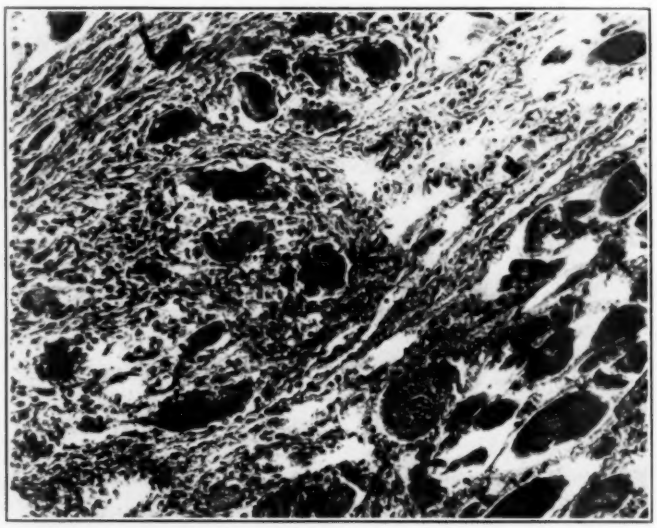

Fig. 1.—Paraspinal muscle of rabbit: necrotic voluntary muscle and inflammatory reaction produced by jet injection, using 0.008 inch bore. Four days following injection (× 230).

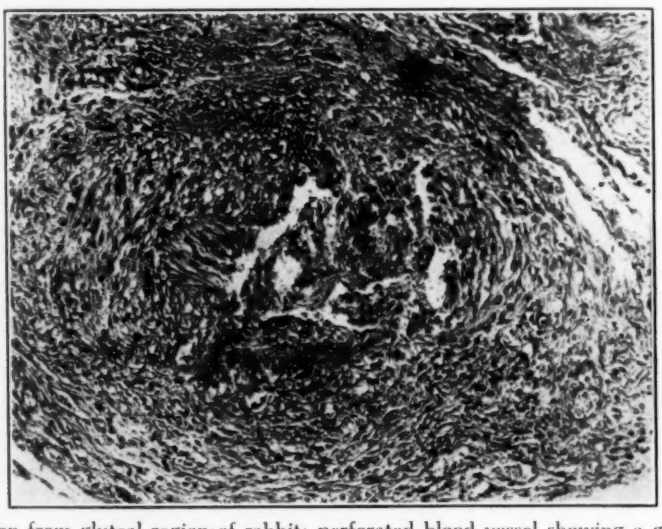

Fig. 2.—Lesion from gluteal region of rabbit: perforated blood vessel showing a granulomatous angiitis produced by jet injection, using 0.006 inch bore. Lesion examined after 5 days (× 145).

ficed at a time when specimens could be obtained at one, 3, 6, and 8 days post-injection. For comparison, intramuscular injections were made in the right paraspinal area with a #21 needle and subcutaneous injections were made with a #21 needle in the left paraspinal area and in both ears.

Two rabbits were injected daily in the paraspinal, thigh, and aural regions with the jet syringe. The animals were sacrificed so that specimens from one to 8 days post-injection might be obtained. Since it was thought that accidental firing of the instrument near the eyes might prove a serious hazard, the jet syringe was fired 7.5 cm. and 15 cm. from the eyes of an additional animal and specimens of cornea were removed for pathological study. The dangers subsequent to misfiring of the instrument over other areas were also evaluated.

Because of probable differences in tissue density and resistance to penetration between the experimental animal and man, a number of jet injections were made in the gluteal region of a fresh cadaver. The sites corresponded to the usual sites for intramuscular injection as well as additional areas along the course of the sciatic nerve and in the inferolateral quadrant of the buttock. Following injection, the areas were incised and then excised *en bloc* to observe depth of penetration as well as the pattern of distribution in the gluteal muscles.

Results. Comparison of heparin absorption rates as manifested by increases in standardized clotting times after 5 to 15 mg. of heparin per kg. body weight did not demonstrate any significant differences in rate of absorption with jet as compared to needle injection. Both methods resulted in clotting time increases within 20 to 40 minutes, depending on the dosage of heparin used.

The 2 rabbits whose tissues were later taken for histological examination were injected a total of 32 times with the jet syringe. Syringe orifices were .004, .006, .008 and .010 of an inch; half of the injections were made with the 2 orifices of smaller bore and half with the larger. Adverse effects were

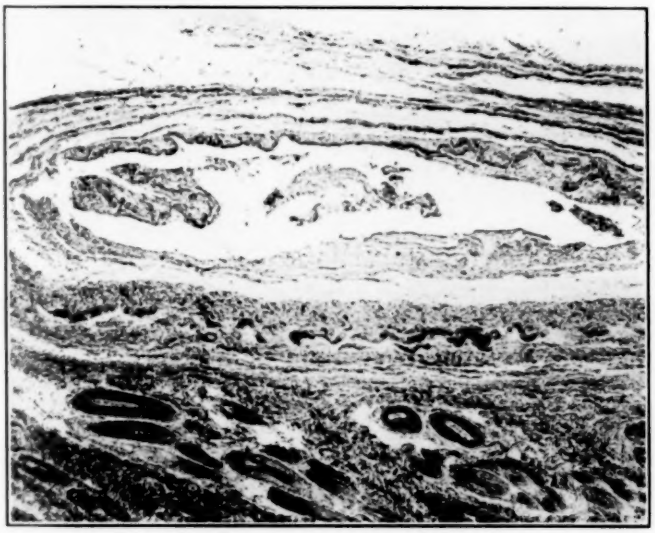

Fig. 3.—Subcutaneous lesion from paraspinal area: pooling of the injectum in a walled-off space in the subcutaneous tissue. Multiple cystic areas of this type were frequently seen in lesions produced by jet injection. Lesion examined 4 days after injection using 0.004 inch bore ($\times$ 55).

noted following 11 of these 32 injections. Although the animals were held firmly while all injections were being performed, slight movement of the animal, even muscle contraction at the site of injection, was sufficient to produce visible skin lacerations in nine instances, accompanied by bleeding in 4, and bleeding alone on 2 other occasions. Lacerations varied in size from one to 15 mm. Eight of these 11 examples of gross tissue trauma occurred when .004 or .006-inch orifices were used.

Gross pathological changes noted at necropsy included several subcutaneous ecchymoses, a superficial hematoma, multiple fascial lacerations, associated in one instance with a large hematoma in an 8 × 10 mm. area of necrotic muscle. Additional injections through the abdominal wall, just prior to necropsy were shown to have penetrated the wall and to have made visible lacerations in bowel, mesentery, and omentum.

Intentional misfiring of the jet syringe 7.5 cm. from one rabbit's eye resulted in a deep laceration in the cornea 1 cm. long. Firing at a 15-cm. distance from the other eye produced a diffuse clouding of the cornea, the surface of which stained well with fluorescein.

No gross damage was seen following any of the injections by needle.

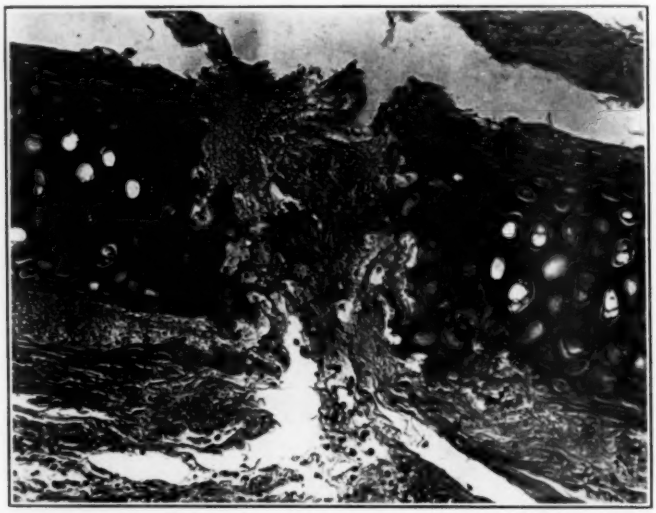

Fig. 4.—Typical early lesion in rabbit ear produced by jet injection, using 0.010 inch bore; perforation of cartilage with pooling of fluid on both sides of the cartilage. These wounds extend through the entire ear. Specimen examined after 3 days (× 160).

Microscopic studies of all lesions produced by the jet syringe and by ordinary injection with 20 and 24 gauge needles were made by multiple step-sections representing the entire area of injury. Composite sketches were made of each lesion. As previously mentioned the lesions were from one to 8-days old.

The lesions produced by jet syringe were destructive to a surprising degree. The wounds of entrance were frequently larger and showed more tissue destruction than those produced from needle injection. The complete perfor-

ations of the ear which characterized the injections by the jet syringe showed even larger wounds of exit than of entrance.

In subcutaneous and deeper tissues the patterns of tissue destruction and inflammatory reactions produced by the jet syringe roughly paralleled the pear-shaped diffusion pattern in contrast to the much smaller linear or fusiform patterns of needle injection. With the jet syringe, tissue disruption, necrosis, and inflammatory response was far greater than with needle injection. Needle injections produced such insignificant injury that the sites of injection were difficult to find. No structure seemed capable of resisting penetration or perforation with the jet injection. Hemorrhage was present in almost every area of jet injection as a result of penetration, perforation, or necrosis of vessel walls. Granulomatous angiitis was present in one wound. Nerve trunks were severed and an early amputation neuroma was seen. The jet syringe injections of the ears perforated the cartilage in every instance with suppurative chondritis as a common complication. Foreign debris frequently was blown into the deep tissues by the jet syringe. Traumatic epithelial inclusions were found. Foreign-body giant-cell reactions about necrotic hairs and other particulate matter were not uncommon. Pooling of the injectum in walled-off spaces was seen only in lesions produced by the jet syringe. Perhaps due to a combination of all of the above features, repair and regeneration were much slower following use of the jet syringe than following needle injection.

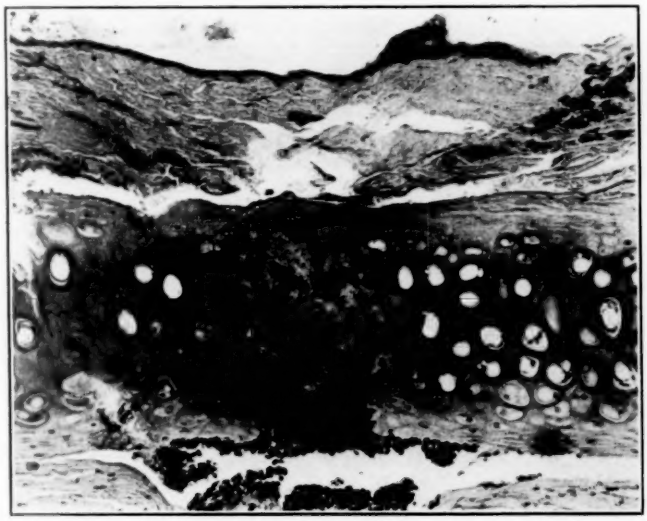

Fig. 5.—A somewhat older lesion in rabbit ear produced by jet injection, using 0.008 inch bore; there is a suppurative chondritis adjacent to the area of perforation. Specimen examined 8 days after injection (× 80).

The recent wounds of the cornea showed widespread denuding of the surface epithelium when the force of the jet syringe was aimed tangentially to the surface from a distance of 15 cm. Perforation and laceration of the cornea resulted when the jet syringe

was aimed more directly at the cornea from a distance of 7.5 cm.

Observations of the results of jet injection in the buttock of the cadaver revealed penetration of the gluteal fascia in all cases. Examination of the muscle revealed dissection by the injectum between muscle bundles with gross disruption of the continuity of the muscle bundles in most instances. Injection over the course of the sciatic nerve at the tubero-trochanteric line produced staining of the nerve with the methylene blue.

Discussion. Results of clinical trials with jet syringes of similar construction have been reported in recent years[1,2,4,5]. Hughes, Jordon, and Hill[6] have listed some of the factors which should be investigated before such instruments can be considered safe and practical for clinical use. Most important, we think, of the fundamental problems is the possible damage to tissues subsequent to such high pressure injections; and secondly, the chance of inadvertent injection directly into veins, arteries, and other important structures. Other factors of lesser importance would include the comparative rapidity of absorption, depth of injection, pain response, and certain technical details yet to be solved concerning amount of injection, mechanical difficulties, and initial instrument cost.

The pear-shaped diffusion pattern of jet-injected material has been demonstrated by other investigators and by the authors. This pattern suggested a wider dispersion of injectum, and, because of this, possible increased rapidity of absorption, a greater chance of inadvertent intravenous injection, and wider extension of potential tissue damage. No difference in absorption rates was found by the techniques used in this study. It was not possible to determine whether small fractions of the injected fluid could have been deposited intravenously; however, the

Fig. 6.—A traumatic epithelial inclusion in the ear of a rabbit resulting from living epithelial cells being blown into the subcutaneous tissues by jet injection. Lesion examined 8 days after injection (× 215).

finding of damage to blood vessels suggests that this consideration cannot be overlooked.

The incidence of visible skin laceration and bleeding in humans following jet injection, as reported by several observers, varies between 7% and 10%. The greater frequency of such complications in this animal study is probably due to occasional slight movements on the part of the animal at the time of injection. Regardless of these gross manifestations of tissue injury, the microscopic lesions reported above, occur, in variable degree, following every jet injection. The tissue damage (hemorrhage, muscle necrosis, nerve injury, inflammatory and foreign body reaction) is sufficiently extensive, and in part irreversible, as to make this instrument unsafe, in our estimation, for clinical use.

Summary. A study was made of the gross and microscopic pathological changes produced by jet injection as compared with needle injection of fluids for subcutaneous administration. No significant difference in the rate of absorption between the two methods was noted. However, injection by means of the jet syringe produced definite tissue damage which, in part, proved to be irreversible, and consequently, it was concluded that the jet syringe employed was unsafe for clinical use.

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THE SUPERIOR VENA CAVA SYNDROME

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The major manifestations of the superior vena cava syndrome are due to conditions which interfere with the flow of blood through the superior vena cava. Essentially the same manifestations are found in bilateral innominate vein obstruction or arteriovenous fistula between the superior vena cava and the ascending aorta. This report will confine itself entirely to obstruction of the superior vena cava. For many years obstruction of the superior vena cava was considered to be a rarity and its description relegated to the realm of rare or unusual clinical findings. Interest in the syndrome has been renewed recently by the perfection of techniques which permit better localization of the obstruction as well as by better clinical descriptions of the nature of the obstruction. In addition, further interest has been stimulated by the advent of relatively new and more aggressive techniques of treatment including radiation and surgery.

The clinical phenomena of superior vena cava obstruction result from the interference with the return flow of blood through the superior vena cava to the right heart. This is manifested by an increased venous pressure in the upper extremities and thorax, delayed circulation time in the upper half of the body and diversion of the main blood stream flow through collateral channels. In addition to these manifestations the primary pathological process which caused the obstruction may cause associated signs as well.

William Hunter is generally credited with the first description of the superior vena cava syndrome. His report appeared in 1757, and described a case of superior vena caval obstruction resulting from an aortic aneurysm. Since that time approximately 400 cases have been reported in the literature, mainly in small groups of cases or individual case reports. The causes of obstruction are many and include aortic aneurysms, primary intrathoracic neoplasms of which over 90% are bronchogenic carcinomas, lymphomas, metastatic carcinoma to the mediastium, mediastinitis due to tuberculosis, syphilis, or pyogenic organisms, thrombosis of the superior vena cava, leukemia, pericarditis, mitral stenosis, pneumothorax and mediastinal emphysema. Approximately 75% of all the reported cases are caused by either primary intrathoracic neoplasms, aortic aneurysms, or lymphomas (See Table 1). Although the incidence of obstruction caused by aortic aneurysms is high in a statistical review of all the reported cases, recent observations have indicated that there has been a spectacular drop in this etiological process. This can be readily explained by the advent of public health measures and effective therapy for syphilis during the past 10 years. The incidence of tuberculous mediastinitis and tuberculous medias-

tinal lymphadenopathy seems to have fallen off as well.

The diagnostic criteria of obstruction of the superior vena cava may be summarized as follows:

1. A significantly elevated venous pressure in the upper half of the body in the presence of normal venous pressure in the lower half of the body.

Relatively simple laboratory aids are available for further elaboration of the cause and location of the obstruction. Phlebography has been described by several authors and is particularly well reviewed by Katz *et al.*[4,9]. It consists of an intravenous injection of a radiopaque material with radiographs taken during and immediately following the completion of the injection. We

TABLE 1

Etiology of obstruction of the superior vena cava in 274 confirmed cases*	*Number*	*Percentage of total*
1. Carcinoma of lung	104	37.9
2. Aortic aneurysms including aneurysm with perforation into superior vena cava	77	28.8
3. "Mediastinitis" including tuberculosis, pyogenic and syphilitic	31	11.3
4. Lymphomas including lymphosarcoma and leukemia	30	10.9
5. Thrombosis of the cava with localized phlebitis either spontaneous or following trauma	16	5.8
6. Primary mediastinal tumors including those from thymus and esophagus	7	2.5
7. Mediastinal metastasis from extrathoracic tumors	4	1.4
8. Propagating thrombi from periphery	2	0.7
9. Pericarditis	2	0.7
10. Mitral stenosis	1	0.3
TOTALS	274	100.%

* Confirmed by necropsy, exploration, biopsy or by sufficient clinical details. This table includes the author's patients.

2. Edema and cyanosis of the face, neck and upper extremities. The cyanosis is usually a peculiar ruddy type of cyanosis and is aggravated by assuming the horizontal position. Many patients complain of a feeling of fullness or congestion in the head[1] after reclining or stooping and these symptoms are relieved upon assuming the upright position (see Fig. 1).
3. Development of collateral circulation which usually includes the observation of visibly dilated superficial veins over the upper half of the body, particularly the chest.

have preferred to use the veins of the antecubital fossa although the external jugular vein could be used as well. The only disadvantage in using the antecubital fossa veins is a possibility of error in interpretation when the obstruction occurs solely in the axillary or brachial veins. A 35% or 70% Diodrast solution is ordinarily used and approximately 30 cc. of the contrast medium is given via a rapid injection. This technique has the advantage of being relatively simple, requiring little preparation or unusual equipment, and is relatively safe. It usually results in an accurate knowledge of the location of the obstruction and

frequently outlines the collateral circulation excellently. On some occasions the nature of the obstruction can be determined or confirmed using phlebography (see Fig. 2).

Roentgenographic techniques including planigrams and multiple views further help to elaborate on the nature of the primary lesion.

Fig. 1.—Photograph of left hand showing the massive amount of edema which may develop in obstruction of the superior vena cava. This patient had a squamous cell carcinoma of the lung which had infiltrated and completely obstructed the superior vena cava.

Infrared photography will frequently graphically demonstrate the extensive collateral circulation particularly if the collateral veins are superficially located (see Fig. 3).

The venous pressure is the best single direct aid in the diagnosis of this syndrome, as well as an aid in following patients particularly in respect to relief of the obstruction or establishment of collateral circulation. Venous pressure is usually taken in the antecubital veins using a 3-way stop cock, spinal manometer and 2½% citrate solution. Hussey *et al.*[3], have described an "exercise test" in which the patient opens and clenches the hand forcefully and repeatedly for one minute while the venous pressure is being measured in the same arm. Normally or in patients with heart failure this exercise test causes little or no change in the venous pressure. If there is obstruction of the venous system through which the arm veins are drained, there is a prompt rise of over 10 mm. of citrate. The venous pressure in the legs is usually normal unless there is concurrent obstruction to the inferior vena cava as well. Hussey *et al.*[3], have also described a paradoxical effect in the oscillation of the liquid in the manometer in relation to the respiratory ef-

forts. Ordinarily in the normal person the liquid level falls slightly on inspiration and rises slightly on expiration. When the superior vena cava is completely obstructed a paradoxical effect may be noted in that column will rise with inspiration and fall slightly with expiration. This is said to be evidence that the principal collateral channels enter the inferior vena cava. In addition, this is also said to be evidence that the level of obstruction is below the origin of the azygos vein where it enters the superior vena cava. Another method described to show the level of obstruction of the superior vena cava clinically is by encircling the lower part of the chest with a constricting band which blocks the superficial veins carrying blood to the inferior vena cava system. If the venous pressure does not rise after this band is inflated or tightened then the obstruction is said to be above the azygos vein and the main collateral circulation is not affected by the superficial constricting band. The circulation time is said to be prolonged in the majority of cases, but we have not found this to be a very helpful test and have included it only for the sake of completeness. Many patients have a normal circulation time despite evidence of extensive collateral circulation and complete

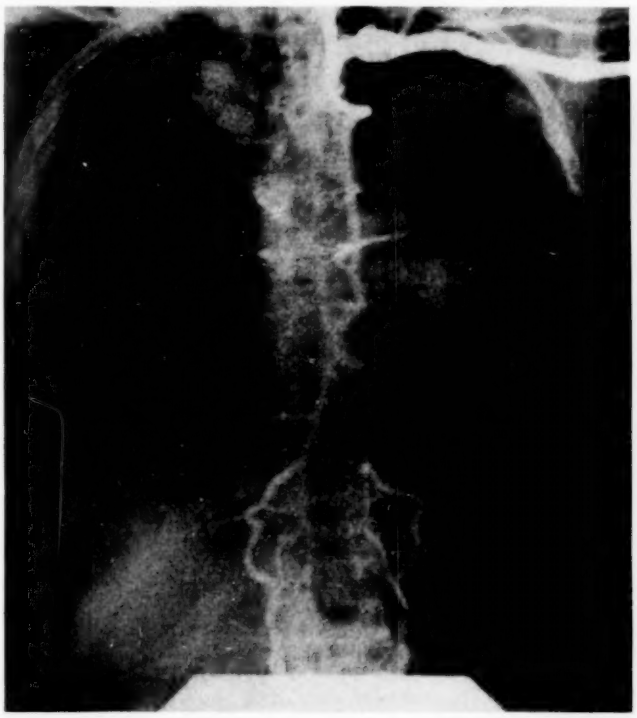

Fig. 2.—Phlebogram showing the level of obstruction beginning at the junction of the left innominate vein and the superior vena cava. Note that the contrast material is shunted through the internal mammary vein to both superficial epigastric veins. This patient had a malignant thymoma.

obstruction of the superior vena cava.

One of the main manifestations of obstruction of the superior vena cava is the collateral diversion of the venous stream with dilatation of certain collateral veins. The superior vena caval system possesses 4 main systems of veins for shunting the blood to the heart around the obstruction. All 4 of the routes are interconnected and all 4 are concerned in the collateral circulation regardless of where the obstruction is although one or 2 routes may be more important than others in various patients. The main consideration is the level of obstruction in reference to the azygos orifice. McIntire and Sykes[5], after Carlson[2] and Quiring[7], have summarized these 4 main routes as follows:

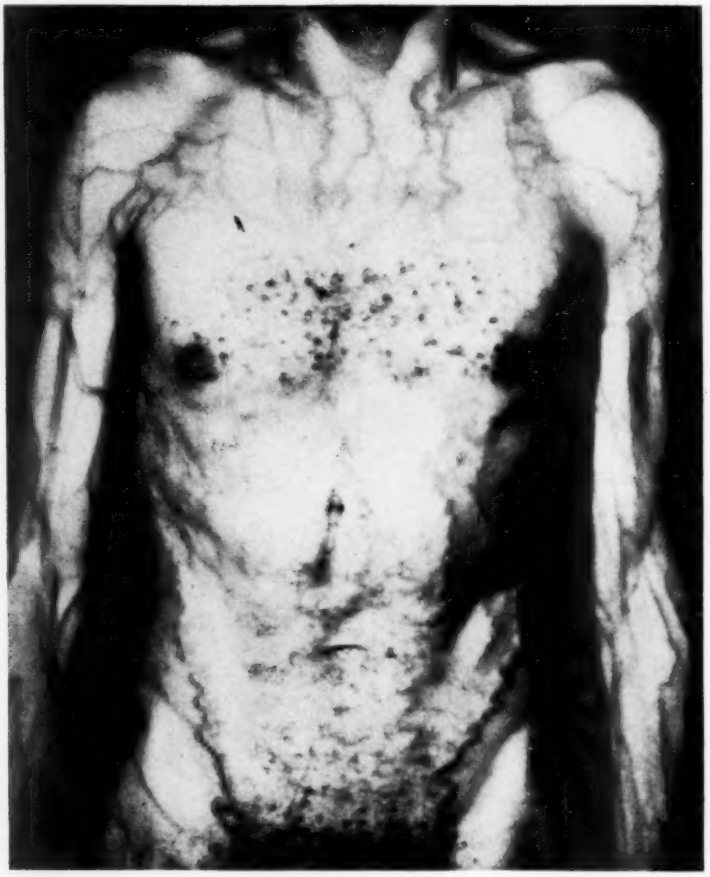

Fig. 3.—Infrared photograph demonstrating the superficial collateral circulation. This patient had an anaplastic bronchogenic carcinoma which had completely infiltrated and obstructed the superior vena cava along its entire length.

1. The azygos route which includes the main azygos, the accessory azygos, ascending lumbar and lumbar veins. These afford a direct communication between the superior and inferior vena cava and are probably the most important

channels returning blood to the heart when the obstruction is above the level of the azygos vein. When the obstruction is below the azygos orifice then the azygos vein diminishes in size and forms a relatively unimportant collateral pathway. Necropsies on patients where the obstruction has spared the azygos orifice have demonstrated that the azygos vein may enlarge tremendously.

2. Internal mammary route. The blood is drained through the internal mammary veins and then through the superior and inferior epigastrics ultimately emptying into the external iliac from which it flows to the inferior vena cava. This is probably the next most important collateral route and occasionally is nicely demonstrated by phlebography (see Fig. 2).
3. The lateral thoracic route. This route consists of the lateral thoracic, thoraco-epigastric, superficial epigastric, and superficial circumflex iliac veins with the blood entering into the femoral vein. These are the veins that are usually seen superficially and are therefore of considerable clinical importance.
4. The vertebral route. This is a deep system composed of the vertebral and intervertebral veins and carries blood from the innominate veins through the dural sinuses to the intercostal, lumbar, and sacral veins ultimately draining into the inferior vena cava.

The majority of the reported cases of superior vena cava obstruction fall within the 40-to 60-year-old age group, because this is the age group in which the main etiological entities are found, namely, bronchogenic carcinoma and aneurysms of the ascending aorta. Eighty per cent of the reported cases occur in males, again because the main etiologic entities are much more common in males. Most of the cases reported in females are due to the statistically lesser important causes including thromboses of the vena cava both spontaneous and due to trauma. Our series of patients had no females because of the selection of admissions to the hospital. The tabular analysis of certain clinical and pathological features as seen in our patients is presented in Table 2. Eighteen of the 22 patients seen had carcinoma of the lung. In 15 of the 18 cases of carcinoma of the lung, the lesion had its origin in either the right main stem bronchus or in the right upper lobe bronchus. This is consistent with a review of the world's literature in which almost all cases of bronchogenic carcinoma of the lung causing obstruction of the superior vena cava arise from the right lung. One case was in a young colored male who had mediastinal and cervical lymph node involvement with active tuberculosis. This patient improved considerably after lymph node biopsy and proper anti-tuberculosis therapy. Only one patient was seen with a luetic aortic aneurysm. This is consistent with the marked decrease in tertiary syphilis now being seen. Obstruction of the superior vena cava is an ominous finding due not to the primary manifestations of venous obstruction but due mainly to the primary pathological etiology causing the obstruction.

In the necropsied patients in our series, dissection revealed infiltration of the superior vena cava by tumor tissue in all but one case of malignant neoplasm. In the 8-year period when our series of patients were observed a total of 210 histologically proven cases of bronchogenic carcinoma were seen.

TABLE 2

Number	*Sex, Race and Age*	*Etiology*	*Cyanosis*	*Superficial collateral circulation*	*Edema*	*Venous pressure (mm. water)*	*How diagnosis confirmed*	*Location and nature of obstruction*
1.	W–M–55	Adenocarcinoma of right lung arising in right main stem bronchus	slight	marked	moderate	300	necropsy	Infiltration of the caval wall by tumor beginning 0.5 cm. from the right auricle and obstructed along its course within the thoracic cavity
2.	W–M–57	Epidermoid carcinoma of the right lung arising in the right main stem bronchus	none	moderate	slight	180	thoracotomy and biopsy	Metastases to mediastinal lymph nodes and direct invasion of the caval wall with obstruction just below origin of both innominate veins
3.	W–M–35	Epidermoid carcinoma right lung arising from right upper lobe bronchus	none	moderate	slight	250	necropsy	Mediastinal invasion with tumor tissue completely encircling and infiltrating the superior vena cava just above the origin of the azygos vein
4.	C–M–55	Adenocarcinoma right lung arising in right upper lobe bronchus	slight	marked	marked	420	necropsy	Mediastinal invasion with tumor tissue invading the superior vena cava from both innominate veins to a point 3.5 cm. from the right auricle
5.	W–M–41	Anaplastic carcinoma right lung arising in posterolateral portion right main stem bronchus	none	moderate	slight	265	necropsy	Infiltration of both innominate veins and superior vena cava to a point 3 cm. from the right auricle
6.	W–M–62	Carcinoma, hilum of right lung	slight	marked	marked	380	clinical	Radiographs revealed a large hilar mass with extension to the superior mediastinum and progressive widening of the superior mediastinum
7.	C–M–23	Tuberculosis, mediastinal lymph nodes	none	slight	none	180	lymph node biopsy	A large nodular mass in the supracardiac region in the superior mediastinum with displacement of the esophagus and trachea posteriorly, and partial obstruction of the superior vena cava by pressure
8.	W–M–61	Epidermoid carcinoma hilum right lung	moderate	marked	slight	340	bronchoscopy with biopsy	Radiographs revealed a large mass adjacent to the right upper lobe bronchus and right paratracheal region with widening of the superior mediastinum

upper lobe bronchus and right paratracheal region with widening of the superior mediastinum

TABLE 2.—(*Continued*)

Number	*Sex, Race and Age*	*Etiology*	*Cyanosis*	*Superficial collateral circulation*	*Edema*	*Venous pressure (mm. water)*	*How diagnosis confirmed*	*Location and nature of obstruction*
9.	W–M–58	Anaplastic carcinoma right lung arising in right main stem bronchus	slight	marked	slight	450	necropsy	Mediastinal metastasis with lymph node involvement and obstruction of superior vena cava by thrombosis and infiltration
10.	C–M–53	Luetic aortic aneurysm	slight	marked	slight	300	clinical	Radiographs show large thoracic aortic aneurysm with some calcification
11.	W–M–57	Lymphoma	marked	marked	marked	550	clinical	Sudden appearance of large superior mediastinal mass presumably obstructing superior vena cava by pressure. (This mass disappeared completely after roentgen-ray therapy and his symptoms of caval obstruction were completely relieved with a drop in venous pressure to 120 mm.)
12.	W–M–52	Adenocarcinoma right lung arising from right main stem bronchus	slight	marked	marked	310	necropsy	Infiltration of wall of superior vena cava with obstruction to a point 4 cm. from right auricle
13.	W–M–51	Adenocarcinoma right lung arising from right main stem bronchus	slight	marked	marked	300	necropsy	Infiltration throughout entire superior vena cava to a point 2 cm. from the right auricle
14.	W–M–24	Malignant thymoma	moderate	moderate	none	600	Exploration and biopsy	Obstruction of the superior vena cava both by infiltration by tumor of the vessel wall and by pressure from the origin of the innominate veins to a point 2 cm. from the auricle
15.	W–M–58	Carcinoma right lung arising in right hilum	slight	marked	none	480	clinical	Radiographs showed a large right hilar mass with extension to and widening of superior mediastinum
16.	W–M–39	Carcinoma right lung arising in right hilum	moderate	moderate	moderate	550	clinical	Radiographs showed a large right hilar mass with extension to and widening of superior mediastinum

TABLE 2.—*(Continued)*

Number	*Sex, Race and Age*	*Etiology*	*Cyanosis*	*Superficial collateral circulation*	*Edema*	*Venous pressure (mm. water)*	*How diagnosis confirmed*	*Location and nature of obstruction*
17.	C–M–55	Anaplastic bronchogenic carcinoma arising in left upper lobe bronchus	slight	marked	moderate	440	necropsy	Extension of the tumor through the mediastinal pleura to involve the pericardium and completely encircling all of the major vessels in this area, and extending through the visceral pleura of the opposite side to involve the apex of the right lung. There was direct infiltration of the wall of the superior vena cava
18.	W–M–35	Squamous cell carcinoma right lung arising in right hilum	moderate	moderate	marked		biopsy and thoracotomy	Large hilar mass with extension to the superior mediastinum and superior vena cava
19.	W–M–27	Adenocarcinoma, left lung arising in left main stem bronchus	none	slight	moderate	220	necropsy	Extension of the tumor into the superior mediastinum completely surrounding the great vessels and infiltrating the wall of the superior vena cava
20.	W–M–48	Adenocarcinoma left lung arising in left main stem bronchus	slight	moderate	moderate	500	necropsy	Extension of the tumor to the mediastinum and to the left innominate vein with complete obstruction of the innominate vein and superior vena cava by tumor thrombus
21.	C–M–54	Anaplastic carcinoma right lung arising in right main stem bronchus	slight	moderate	slight	210	necropsy	Extension of tumor to the lymph nodes of the superior mediastinum with compression of the superior vena cava by a solid mass of large nodes. There was no direct infiltration of the vein found
22.	W–M–38	Adenocarcinoma right lung arising in right main stem bronchus	moderate	marked	marked	470	necropsy	Spread of the tumor by direct extension to the mediastinum completely encircling and invading the superior vena cava. Tumor thrombi were found in the lumen from the right atrium to the origin of the innominate veins

This represents an incidence of 11% of superior vena cava involvement as a complication in primary carcinoma of the lung. Spontaneous thromboses or thromboses following trauma to the chest have been reported and were extensively reviewed by Ochsner and Dixon[6]. This cause of the superior vena cava syndrome is a rare and unusual entity. When it does occur, patients have been reported to live for many years without undue difficulty. The syndrome of obstruction of the superior vena cava can also be caused by an arteriovenous fistula between the ascending aorta and the superior vena cava. This has not been reviewed in this paper.

Rosenbloom[5] reviewed superior vena cava obstruction in primary carcinoma of the lung and added 8 cases to the literature, but unfortunately did not elaborate on the nature of the obstruction in his necropsied patients. In patients with malignant intrathoracic neoplasms the obstruction of the superior vena cava is generally caused by infiltration of the venous wall by tumor tissue with both tumor and secondary thromboses.

Considerable mention is made of the danger of bronchoscopy, anesthesia, excitement and other factors which might cause intracranial rupture of the draining veins. Although this is a distinct rational possibility with the markedly increased venous pressure, distended veins, and stasis of blood flow we have not observed this complication in any one of our patients. A review of the literature failed to elaborate any further on this question and we are of the opinion that this complication does not occur as frequently as is feared. The walls of the veins are capable of considerable distention without rupture and this is probably the reason that such intercranial accidents are not seen.

Summary. A review of the superior vena cava syndrome as caused by obstruction of the superior vena cava is made. The major manifestations found in this syndrome include cyanosis and edema of the face, neck and upper extremities, markedly elevated venous pressure in the upper extremities with a normal venous pressure in the lower extremities, and distention of the superficial veins of the upper portion of the body with the flow being caudad. A table showing the important and interesting features in our series of 22 patients seen in recent years is presented. Almost all cases of superior vena caval obstruction by intrathoracic malignant tumors are caused by direct invasion of the venous wall by tumor tissue. A considerable decrease in the incidence of obstruction caused by aneurysms of the ascending aorta is now being seen and it is likely that this cause of superior vena cava obstruction will become relatively unimportant in future years. Techniques for aiding in the diagnosis, localization and elaboration as to the nature of the obstruction are described. Because of the ability of veins to distend and enlarge without rupture, intracranial hemorrhage is relatively rare despite the markedly increased pressure within the collateral veins. The syndrome of superior vena cava obstruction is not nearly as rare as was formerly believed, and should be searched for and studied more frequently. We found an incidence of 11% involvement and obstruction of the superior vena cava in primary carcinoma of the lung.

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THE USE OF APRESOLINE IN THE HYPERTENSIVE ARTERIOSCLEROTIC SYNDROME*

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Treatment of hypertension in the elderly patient is rarely undertaken with any enthusiasm. Usually survival to older age in these individuals means either mild disease which does not warrant the use of potent hypotensive agents or an apparently irreversible situation which is most frequently a cerebrovascular accident. The added factor of arteriosclerosis and the danger of reducing the hydrostatic pressure when there may already be a reduced blood flow in the cerebral, coronary and renal arteries, adds another deterrent to intensive hypotensive therapy with many of the available drugs.

Recent data[1] indicate, however, that the changes in the vascular system in the aged are not completely irreversible. Thus, while the cerebral blood flow is usually reduced in the elderly subject, the response to agents known to produce cerebrovascular dilatation (such as carbon dioxide) is qualitatively, though not quantitatively, similar to that elicited in the younger subject. Recent reports[3,7,9] indicate that l-hydrazinophthalazine hydrochloride (Apresoline) augments renal flow and cardiac output and decreases cerebral vascular resistance while producing a fall in hydrostatic pressure. It would seem worthwhile, therefore, to evaluate Apresoline in the aged patient with persistent diastolic hypertension.

Material and Methods. All subjects in this study were residents of an institution for the aged. They included 10 women and 7 men, ranging in age from 51 to 81 years, with persistent diastolic hypertension, and an additional 2 men and 1 woman, ranging in age from 79 to 91 years, with symptomatic arteriosclerosis and cerebral insufficiency but an essentially normal blood pressure range.

Although many of the subjects exhibited electrocardiographic evidence of coronary disease, only one had a history of coronary insufficiency. Similarly, many patients had objective evidence of occlusive peripheral vascular disease, but it presented a problem in only one individual. Congestive circulatory failure was present prior to this study in only 2 patients, and, while the elevated blood urea nitrogen determinations in several individuals implied impaired renal function, it offered no problem in clinical management. By far the most frequent disability, and the common denominator in this group, was cerebral insufficiency (senile psychosis and/or psychosis with cerebral arteriosclerosis) which

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Apresoline supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

provided the necessity for institutional care in most of these individuals.

The patients were seen by the physician only with the same frequency as other residents of the institution, and the clinical evaluation was based largely on daily "report cards" completed by the nursing staff. On these "report cards" certain complaints felt to be significant, such as headaches, visual disturbances, giddiness, weakness in the legs, were quantitated on the basis of zero if absent, and 1 to 4 if present. Additional complaints were recorded as such.

All blood pressure determinations were made twice daily by the same nurse using the standard sphygmomanometric technique. In addition to the routine history and physical, each patient had a blood urea nitrogen determination, electrocardiogram, a 2-meter chest film when possible, and studies of cerebral hemodynamics and metabolism. The nitrous oxide procedure for the determination of cerebral blood flow as devised by Kety and Schmidt[5] and modified by Scheinberg and Stead[8] was employed. Values for cerebral blood flow, cerebral vascular resistance, and cerebral metabolic rate were calculated as described by the above authors. Mean arterial pressure was read from a damped aneroid manometer attached to a needle in the femoral artery. Blood-gas analyses were performed according to the manometric technique of Van Slyke and Neill[6].

After completion of the control studies, Apresoline therapy was instituted, initially 25 mg. 4 times daily, and increased 25 mg. per dose every 2 to 5 days until either the desired effect had been achieved or until there was no further fall in pressure. In several individuals this dosage was further increased to determine whether any untoward effect would develop with larger concentrations. In about half of the patients, placebo was substituted for Apresoline for a variable period, the duration of which was determined by the clinical course, and this was followed by reinstitution of Apresoline as indicated below. The dosage of the latter was the same as that which the patient had received prior to placebo and represented the "effective dose" of Apresoline for that patient.

The experimental blood pressure range was determined by averaging the blood pressure recorded during the arbitrarily-selected calendar period for the group as a whole. The baseline procedures were repeated during this period.

Results. 1. EFFECTIVENESS OF APRESOLINE IN REDUCING BLOOD PRESSURE. *Dosage.* The effective dose, that is, the total daily amount of Apresoline inducing the maximal depression of blood pressure, varied from 200 to 600 mg., but up to 1,300 mg. were given. In our experience, if the patient tolerated the drug, he would tolerate dosages much greater than that necessary to give the maximal response.

A general summary is presented in Table 1. Treatment with Apresoline was discontinued in one of the initial 17 hypertensive patients because of drug intolerance. Of the remaining 16 patients, 14 were significantly improved. The depression in average blood pressure in the 14 patients significantly improved was 45 mm. Hg systolic and 26 mm. Hg diastolic. The remaining 2 patients, H. N. and J. N., were not considered to be improved at the time of the experimental determination despite a fall in average blood pressure.

All 3 patients who were considered primarily arteriosclerotic and whose blood pressure range fell in general within normal limits, exhibited a fall in blood pressure on Apresoline, but the depression was somewhat lower than that exhibited in the hypertensive group and averaged 32 mm. Hg systolic, 19 mm. Hg diastolic.

In 7 of the 14 improved hypertensive patients and 1 of the 3 arteriosclerotic patients, placebo was substituted for the Apresoline. In the majority, the blood pressure tended to return gradually to pre-treatment levels. In 4 of the hypertensive patients, Apresoline therapy had to be reinstituted because of acute episodes of hypertensive encephalopathy developing within 2 to 60 days. Three of these 4 improved but 1 died. The one arteriosclerotic patient succumbed while on placebo therapy.

2. CEREBRAL HEMODYNAMICS AND METABOLISM. During the control period and after the effective Apresoline dosage had been established, cerebral

TABLE 1. SUMMARY OF CLINICAL DATA

Patient	*Age*	*Duration of Hypertension (years)*		*Clinical Observations**	*BUN*		*Blood Pressure Range**
C. B.	64	14	C	Multiple CVA's with residual paraplegic headaches.	16	C	197/102
			A	Remission in headaches.	17	A	141/78
			P	Acute episodes of severe headache, mental confusion, speech impairment.		P	176/98
			A	Remission in all symptoms & signs except residual paraplegia.		A	156/81
N. B.	66	35	C	Residual left hemiparesis, mental deterioration, apathy, antagonism headaches, and giddiness.	8	C	157/97
			A	Increased headaches, palpitation, moderate improvement in mental status.	12	A	137/82
			P	Semi-comatose.		P	160/105
			A	Remission in all complaints; patient agreeable and cooperative, residual hemiparesis unchanged.		A	141/81
C. B.	69	8	C	Residual left hemiparesis, headaches and giddiness, staggering, persistent pain in left upper and lower extremities, disagreeable sensation in mouth.	13	C	164/103
			A	Remission in all abnormalities except mouth sensation, no change in hemiparesis.	22 22	A	124/76
			P	Acute episode of weakness with return of all symptoms.		P	170/110
			A	Remission except mouth sensation and hemiparesis.		A	121/73
M. S.	69	10	C	10-yr. history of episodes of headaches and blind staggers, frequent bouts of pyelonephritis, more recently mental deterioration & enuresis.	17–21	C	159/105
			A	Marked improvement in personality with interest in church, social activities, etc., no further headaches or blind staggers.	18–24	A	123/82
			P	Gradual mental retardation; semi-comatose, expired.		P	164/107
F. W.	70	3+	C	Abnormal behavior pattern, apathetic, disoriented.	20	C	230/117
			A	Oriented, alert.	20–18	A	183/90
			P	Confused, delusions, disoriented.		P	210/102
E. B.	57	10	C	Headaches.	8	C	152/98
			A	Remission in headaches.	12	A	124/81
			P	No change, no recurrence of headaches.		P	145/89
N. D.	81	2+	C	Residual right hemiparesis, apathetic, confused, disoriented.	16	C	193/102
			A	Alert, oriented, remission in pain, no change in hemiparesis.	17	A	141/75
			P	Gradual return to previous mental status.		P	184/94
			A	Again oriented and alert.			

TABLE 1.—(*Continued*)

Patient	*Age*	*Duration of Hypertension (years)*		*Clinical Observations**	*BUN*		*Blood Pressure Range**
H. N.	51	2+	C	Multiple CVA's with left hemiplegia, apathetic, depressed.		C	198/110
			A	Improved mental situation but probably secondary to many factors, escape from Apresoline under stress with acute rise in B. P. to 220/120 and demise.		A	173/94
L. L.	64	15	C	3-yr. history of intermittent congestive circulatory failure (compensated at this time), marked weakness in legs and staggering gait, apathetic, probable posterior wall myocardial infarction.	22–24	C	209/124
			A	Marked improvement, gait normal, no further complaints, patient personable and enthusiastic, one episode of substernal pain.	27	A	129/74
M. B.	71	1+	C	Headaches, dizziness.	20–19	C	201/114
			A	Complete remission.	24–24	A	149/85
B. W.	73	1	C	Senile psychosis, serology positive, central nervous system syphilis.	10	C	171/102
			A	No change.	16	A	125/71
H. S.	75	2+	C	Psychotic, garrulous, pathologically euphoric, rheumatoid arthritis.	21–15	C	200/105
			A	Gradual improvement with disappearance of garrulousness and euphoria, rheumatoid arthritis unchanged.	16–16	A	140/73
M. T.	71	2+	C	Hemiplegia, intermittent congestive circulatory failure, no mental abnormalities.	18–18	C	183/99
			A	Onset congestive circulatory failure following discontinuance of failure regimen.	19	A	147/83
J. N.	72	1+	C	Severe arteriosclerotic obliterans, absent right leg, occipital headaches.		C	169/105
			A	No significant improvement.		A	148/89
B. I.**	57	7	C	Multiple CVA's with residual motor weakness, congestive failure compensated, slurred speech, dizziness, staggering gait.	11	C	201/115
			A	Increase in all complaints particularly headaches and dizziness, Apresoline discontinued.			
M. O.	68	2+	C	Rheumatoid arthritis, severe, mentally alert.	8	C	191/99
			A	No change.	25	A	136/71
S. A.	66	2+	C	No significant abnormalities.	7	C	184/105
			A	No change.	11	A	146/79

TABLE 1.—(*Continued*)

Patient	*Age*	*Duration of Hypertension (years)*	*Clinical Observations**	*BUN*	*Blood Pressure Range**
W. G.‡	91		C Dizziness, weakness in legs.	18	C 148/82
			A Remission of dizziness, some improvement in leg weakness, one episode of substernal pain with freq. premature ventricular contractions.	22	A 97/60
C. B.‡	82		C Dizziness, weakness in lower extremities, staggering gait.	11	C 153/82
			A No further dizziness, increased strength in lower extremities, no further staggering.	13	A 139/66
M. C.‡	79		C CVA with residual left hemiparesis, mentally alert.		C 157/90
			A "Felt better," improved appetite, slept better.	20–18	A 120/71
			P Patient became apathetic, lethargic, expired.		

* C indicates control; A, Apresoline; P, Placebos.
** Drug discontinued because of intolerance.
‡ Arteriosclerotic subjects.

hemodynamics and metabolism studies were performed. The results are recorded in Table 2.

In all patients except one (M. T.), there was either no change or an increase in cerebral blood flow. A decrease in cerebrovascular resistance after Apresoline was noted in all subjects except M. T. The mean control cerebral blood flow (cc./min./100 gm. of brain) was 43.6; the experimental flow was 53.6, an increase of 23%. The mean cerebrovascular resistance (mm. Hg/cc. blood/min./100 gm. of brain) in the control period was 3.4 with a fall to 2.5 during Apresoline therapy, a 26.5% reduction. The mean cerebral metabolic rate was not significantly changed as a result of Apresoline. The cerebral arteriovenous oxygen difference of the control subjects is less than that for normal young subjects. Apresoline administration caused a reduction of about 20% of the mean cerebral arteriovenous difference: a finding consistent with the increase of cerebral blood flow, and no change in the cerebral oxygen utilization. The mean arterial pressure as recorded directly from the femoral artery at the time of cerebral blood flow estimations fell from a control of 142 mm. Hg to 125 mm. Hg. Unfortunately, repeat determinations in the placebo group during their rebound period could not be obtained.

Discussion. It is apparent that Apresoline causes a moderate but significant reduction in both systolic and diastolic pressures of elderly subjects with hypertensive arteriosclerotic syndrome and those with arteriosclerosis alone. The values noted for mean arterial pressure are somewhat higher than those recorded daily by the sphygmomanometric procedure. The difference may be due to the apprehension and discomfort associated with the cerebral blood flow procedure at which time the mean arterial pressures were taken. Apparently Apresoline in the concentrations used was not totally effective

in completely blocking the effects of noxious stimuli. Contrary to previous reports, undesirable side effects were either absent or of insufficient magnitude to be disturbing to our subjects.

It has been previously demonstrated in younger subjects[4] that when the blood pressure is moderately reduced (sympathetic block), cerebral vessels dilate and cerebral blood flow and oxygen consumption may be maintained within normal limits. In the present study, despite the reduction of mean arterial pressure, there was a moderate increase of the mean cerebral blood flow and a significant decrease of mean cerebral vascular resistance and no change in cerebral oxygen utilization during Apresoline therapy. Hafkenschiel[3] has previously reported a significant decrease of cerebral vascular resistance and no change in the rate of cerebral blood flow of young hypertensive subjects one hour after the injection of Apresoline intramuscularly. The fact that Apresoline was also effective in reducing the cerebral vascular resistance in elderly hypertensive subjects with cerebral arteriosclerosis is particularly significant. It again indicates that the cerebral vessels of such subjects are capable of compensating for a moderate reduction of pressure by increasing their diameter. The mean reduction of cerebral vascular resistance of 25% is approximately the same as noted by Hafkenschiel in his subjects.

TABLE 2.—EFFECT OF APRESOLINE ON CEREBRAL HEMODYNAMICS AND METABOLISM

		CBF		*CVR*		*$CMRO_2$*		*CDO_2*		*$A\text{–}VO_2$*		*MAP*	
Patient	*Age*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*
M. D.	71	47.0	50.4	3.5	3.2	1.9	2.0	5.6	5.7	4.02	4.01	164	162
B. W.	73	37.2	78.3	3.6	1.3	1.8	2.0	5.9	11.4	4.83	2.52	134	100
H. S.	75	49.1	71.0	2.9	1.7	2.2	2.2	6.3	9.1	4.55	3.14	140	120
M. O.	68	40.9	57.9	3.6	2.4	1.5	1.5	4.0	5.8	3.60	2.54	148	140
M. T.	71	43.7	33.2	3.1	3.6	2.2	2.1	5.6	4.3	5.12	6.42	133	120
J. N.	68	57.9	65.1	2.2	1.7	3.1	2.8	6.5	7.4	5.29	4.24	127	108
H. N.	51	39.0	52.4	4.7	2.5	1.4	1.4	6.1	7.1	3.57	2.68	184	130
L. L.	64	33.0	50.6	4.4	2.2	1.8	2.4	5.5	6.8	5.54	4.83	146	110
F. W.	70	45.2	49.0	4.6	3.7	1.3	0.9	6.5	7.2	2.95	1.85	208	180
E. B.	57	37.1	40.6	3.4	2.9	1.9	1.6	5.2	5.1	5.14	3.97	127	117
N. D.	81	42.1	51.6	2.9	2.1	2.7	2.3	5.2	6.3	6.39	4.44	120	110
C. B.	69	58.6	62.0	1.8	1.7	2.9	3.1	7.5	7.6	4.93	4.87	108	107
M. S.	69	47.5	49.1	3.1	2.3	3.0	1.6	5.7	5.5	6.24	3.12	147	116
C. B.	64	58.2	61.0	2.7	2.5	1.9	2.2	8.8	8.9	3.30	3.56	158	150
N. B.	66	23.6	27.6	5.2	4.5	1.3	1.4	3.6	4.2	5.64	5.01	122	124
W. G.	91	40.9	64.5	3.5	1.9	1.7	2.6	5.1	7.6	4.14	4.20	142	114
M. C.	79	39.4	46.7	2.9	2.5	2.0	1.3	4.0	4.9	5.13	2.73	113	116
						Mean Values							
	70	43.6	53.6*	3.4	2.5†	2.0	2.0	5.7	6.8	4.73	3.77*	142	125*

CBF signifies cerebral blood flow in cc./min./100 gm. of brain; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. of brain; $CMRO_2$, cerebral oxygen consumption in cc./min./100 gm. of brain; CDO_2, cerebral oxygen delivery in cc./min./100 gm. of brain; $A\text{–}VO_2$, cerebral arteriovenous oxygen difference in volumes per cent; MAP, mean arterial blood pressure in mm. of Hg. C indicates control and E, experimental.

* $P < .05$

† $P < .01$

Our data threw no light on the mechanism by which Apresoline induces cerebral vasodilatation. In view of the fact that the fall in cerebral vascular resistance occurs despite a reduction of arterial carbon dioxide tension[3] and since sympathetic vasoconstrictor reflexes seem to have little influence on cerebral vascular tone, it appears most likely that it may act by inhibiting pressor substances.

The moderate increase in mean cerebral blood flow noted in our subjects suggests that factors other than simple compensation for a reduction in pressure must occur after Apresoline. An increase in renal and peripheral blood flow has also been reported after its administration. Perhaps the increase of cardiac output attendant with its use may explain the increase in cerebral blood flow.

Our results confirm the observation of a lowered cerebral metabolic rate in subjects with senile psychosis[2]. It is interesting that despite an increased oxygen delivery there was no change in cerebral oxygen utilization.

The most dramatic and unexpected change observed in these patients was the marked improvement in the manifestations attributed to cerebral insufficiency. Eleven of the group of 14 hypertensive patients exhibited such manifestations. These varied from dizziness, weakness in legs, unsteadiness with staggering gait, to apathy, mental deterioration, confusion, disorientation and delusions. One might be tempted to conclude that the improvement observed was due to the increase of cerebral blood flow and the increase of oxygen delivery to cerebral cells. There is no conclusive evidence, however, that the cerebral cells of elderly subjects suffer from a chronic oxygen insufficiency. Cerebral blood flow, though reduced from normal in these subjects, is still significantly above the rate at which one observes signs of cerebral ischemia. Furthermore, much more oxygen could be extracted by the cerebral cells of elderly subjects if required, as evidenced by the rather high oxygen content of the cerebral venous blood suggesting more than adequate oxygen tension. If the existing cellular pathology is due to causes other than vascular insufficiency (enzymatic), an increase of cerebral blood flow and oxygen delivery would serve no useful purpose.

One cannot conclude, however, that since the cerebral oxygen consumption was not significantly increased following Apresoline therapy, cellular energy production or utilization was not improved. Since the procedure used for estimating cerebral metabolic rate measures the oxygen consumption of the entire brain, it may not reflect improved oxygen utilization of certain areas of the brain. Furthermore, the changes in cerebral oxygen consumption required for improved function may be so slight that they cannot be detected by available methods.

When one reviews the individual cases of the series presented, it becomes obvious that there is no good correlation between the rate of cerebral blood flow and clinical status either before or after Apresoline therapy. In some of the patients before therapy, cerebral blood flow was below normal, and despite no significant change after Apresoline, marked subjective improvement was noted. This would seem to indicate that the observed improvement in mental status with Apresoline may not be directly related to hemodynamic changes.

Summary. Apresoline was administered to 17 elderly hypertensive arteriosclerotic subjects for 5 to 7 months in concentrations that caused a significant reduction of both systolic and diastolic

pressures. Despite the large doses given (400 to 1,300 mg.), in only one patient was it necessary to discontinue the drug because of distressing side effects. No cerebral or cardiac complications were noted. The mean value for cerebral blood flow increased after Apresoline and the cerebral vascular resistance decreased suggesting a direct relaxing effect of the drug on cerebral vessels. The cerebral metabolic rate remained unchanged. While receiving Apresoline many of the subjects appeared to be clinically improved, and upon substituting placebos for the Apresoline, deterioration became apparent. The significance of these findings is discussed.

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THE EFFECT OF POTASSIUM DEPLETION INDUCED BY DESOXYCORTICOSTERONE ACETATE ON THE LETHAL DOSE OF LANATOSIDE C IN DOGS: RELATIONSHIP OF PLASMA LEVELS, SKELETAL AND CARDIAC MUSCLE POTASSIUM CONTENT TO THE LETHAL DOSE

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The relationship between potassium and the action of digitalis has been a subject of increasing interest. It was shown by Baker[2] and Friedman and Bine[16] that increased potassium concentration protects the experimental animal and the perfused heart against the toxic effects of digitalis glycosides. This knowledge has been applied to the human by Enselberg, Simmons, and Mintz[13], Sampson, Alberton and Kondo[27], and others[5,8] who have used potassium salts effectively in the treatment of ectopic rhythms resulting from digitalis toxicity.

Conversely, potassium depletion has been found to have a potentiating effect on the action of digitalis[16]. Lown and his co-workers[22] induced potassium loss in 10 patients with congestive heart failure by the use of mercurial diuretics combined with ammonium chloride, injections of desoxycorticosterone acetate (DOCA) and intravenous infusions of glucose and insulin. They measured the amount of digitalis necessary to produce electrocardiographic evidence of digitalis toxicity, as manifested by ventricular extrasystoles, impairment of auriculoventricular conduction or alterations in the pacemaker, before and after potassium depletion. Toxic effects appeared after smaller doses of digitalis in patients who were in negative potassium balance despite the fact that serum potassium levels were not significantly affected. It was inferred that alterations in intracellular potassium distribution were probably responsible for the increased sensitivity to digitalis. In a similar experiment[23] the artificial kidney was used to produce selective potassium depletion in dogs. These animals developed ventricular extrasystoles and ventricular tachycardia with smaller doses of digitalis after potassium depletion than was required before the artificial kidney was used. The clinical implications of this relationship were reported by Kraus[21] and Hay and Wood[20] who noted the development of digitalis toxicity in digitalized patients who were depleted of potassium during ammonium cation exchange resin therapy.

Conflicting evidence has been presented with regard to the closely related problem of the effect of digitalis on the potassium content of the myo-

cardium. Many investigators[1,4,7,16,18,31] have found a diminished potassium content in animal heart muscle after the administration of digitalis in toxic or fatal doses. Smaller quantities of digitalis, however, comparable to therapeutic doses in humans, produced definite increases in heart muscle potassium according to Boyer and Poindexter[4] and Hagen[18]. Additional evidence in this direction has been presented recently by Clarke and Mosher[9]. They found that the potassium content of heart muscle obtained at necropsy was below normal in undigitalized cardiac patients and normal or near normal in those who had been receiving therapeutic doses of digitalis. On the other hand, Sherrod[28] noted significant potassium depletion in auricular muscle but no significant change in the potassium content of ventricular muscle following rapidly administered lethal doses of tincture of digitalis in animals.

In some of the experiments referred to above[4,7], however, vomiting due to toxic or lethal doses could well have been responsible for the potassium depletion rather than the digitalis itself. Furthermore, when isolated perfused hearts or heart lung preparations were used[18,29,31], it is problematical whether the results are strictly applicable to those obtained in the intact animal.

The purpose of the present experiment was threefold: 1) to obtain additional evidence with regard to the effects of lowered body concentrations of potassium on digitalis sensitivity by determining the lethal dose of a glycoside in control dogs and potassium depleted dogs; 2) to determine whether tolerance to digitalis is related more closely to "extracellular potassium" as reflected by potassium levels or to "intracellular potassium" as reflected by skeletal and cardiac muscle potassium content; and 3) to obtain additional information relative to the effect of digitalis on the myocardial potassium content.

Experimental Methods. The lethal dose of lanatoside C was determined in the following 3 groups of dogs using a modification of the method of Burn[6].

GROUP I: Nine normal dogs.

GROUP II: Ten potassium depleted dogs which had received 25 mg. of DOCA intramuscularly daily for from 12 to 26 days and, in addition, approximately 0.3% sodium chloride solution with the drinking water[19,26].

GROUP III: Five dogs to whom DOCA was administered for from 13 to 17 days. In addition, these animals received 0.15 to 0.2% potassium chloride solution as drinking water to prevent the development of potassium depletion[15]. They received no sodium chloride.

GROUP IV: Four normal dogs were treated in the same manner as Group I with the exception that the femoral vein infusion did not contain lanatoside C. These animals were killed within 30 to 40 minutes by air injection. Group IV was used to obtain "normal" values for skeletal muscle and heart muscle sodium and potassium content after death by our methods.

Healthy mongrel dogs weighing 10 to 13 kg. were assigned to the 3 groups at random (Groups I-III). The dogs which were given DOCA were also given anti-distemper serum and deworming capsules to prevent sickness during the several weeks required for potassium depletion. Many of these dogs spontaneously developed a certain degree of potassium deficiency. No attempt was made to reduce the potassium content of the food because of the tendency of dogs to starve rather than eat low potassium diets.

Powdered dry lanatoside C of uniform potency was dissolved in 70% alcohol to make a stock solution containing 1 mg. per cc. This was stored in the refrigerator in a ground glass bottle. A 5 to 10 cc. aliquot was diluted with 10 parts of distilled water before each day's experiment. The dogs were kept under light anesthesia and artificial respiration was given during the experiment. The diluted lanatoside C containing 0.1 mg. per cc. was delivered into the femoral vein by constant drip at a rate of 1 cc. (0.1 mg.) per minute. Death from ventricular fibrillation resulted in from 20 to 45 minutes. Femoral artery blood pressure was recorded continuously and in most of the animals frequent electrocardiograms were taken. The time of death was recorded at the point where

the blood pressure dropped precipitously to the base line without subsequent rise. Electrocardiograms recorded at this time showed the onset of ventricular fibrillation. This end point was sharp and unmistakable in all the animals. The lethal dose is expressed in mg. of lanatoside C per kg. of body weight (Table 1).

Plasma sodium and potassium were determined before the administration of lanatoside C in the control dogs, and after DOCA, but before lanatoside C in the dogs of Groups II and III. All plasma samples obtained just before or immediately after death showed variable degrees of hemolysis and for this reason we did not attempt to determine the plasma electrolytes after lanatoside C. Skeletal muscle sodium and potassium were studied before and after the glycoside was administered in the control dogs and the DOCA treated dogs. The right and left ventricular muscle was also analyzed for sodium and potassium. Biopsies obtained just prior to the administration of lanatoside C were done under light anesthesia. All control skeletal muscle biopsies were obtained from the muscle of the medial aspect of the thigh; some of the muscle samples obtained after death were from the pectoralis group.

TABLE 1.—PLASMA ELECTROLYTES IN CONTROL AND IN EXPERIMENTAL ANIMALS

Dog	*Weight in kg.*	*Days on DOCA*	*Control K mEq./L.*	*Control Na mEq./L.*	*K after DOCA*	*Na after DOCA*	*Lethal Dose Lanatoside C; mg./kg. body weight*
			Group I: Control Dogs				
7	12.2		3.8	153			0.32
9	12.6		3.6	135			0.31
12	10.5		4.3	158			0.24
13	11.1		3.9	148			0.37
17	11.7		3.6	158			0.32
18	13.3		4.0	163			0.26
22	10.9		4.1	157			0.34
26	12.5		4.1	150			0.26
27	11.8		3.8	161			0.29
Mean	11.7		3.9	154			0.30
			Group II: Dogs Receiving DOCA				
2	9.2	26	3.5	158	2.5	162	0.28
3	12.9	14	3.8	145	2.3	139	0.21
4	13.0	15	3.3	159	2.1	152	0.23
5	10.3	21	3.6	144	2.2	170	0.20
6	12.4	24	4.8	147	3.9	161	0.26
14	8.9	13	4.5	150	2.1	162	0.27
15	9.3	13	3.7	152	1.7	166	0.27
21	11.2	14	3.6	152	2.2	165	0.31
24	9.5	21	3.3	151	2.7	147	0.29
25	12.3	12	3.6	156	1.8	152	0.32
Mean	10.9		3.8	153	2.36	157.7	0.26
			Group III: Dogs Receiving DOCA plus KCl				
10	14.2	17	4.2	153	3.2	163	0.25
11	13.1	17	3.1	141	3.1	154	0.25
19	10.6	13	3.8	147	3.0	157	0.30
23	11.5	16	4.6	156	3.9	151	0.32
28	9.6	14	3.5	154	3.2	164	0.31
Mean	11.8		3.8	150	3.3	158	0.29

Analytic Methods. Plasma sodium and potassium were determined on heparinized plasma using the Beckman Model D-U spectrophotometer with flame attachment[3]. Duplicate readings were made on a single aliquot of plasma.

To 1 cc. of plasma, 4 cc. of 10% trichloroacetic acid and 5 cc. of distilled water were added. This was filtered and the potassium determination was run on the filtrate. One-

half cubic centimeter of filtrate was diluted to 10 cc. with distilled water in a volumetric flask, and this diluted filtrate was used for the sodium determination. The potassium standards were made up containing 13.05 mEq./L of sodium which approximated the concentration of that ion in a 1 to 10 dilution of normal plasma. The sodium standards contained only sodium. All standard solutions contained trichloroacetic acid in the same concentration as in the unknown.

The muscle specimens were stored in the freezing compartment of the refrigerator at a temperature of −9° C. until the analysis could be run. After thawing, the tissue was patted with moist gauze to remove surface blood. A piece of muscle weighing approximately 1 to 1.5 gm. was freed of visible fat, minced and divided into 4 aliquots. As rapidly as possible, the aliquots were placed into 4 previously weighed dry tubes and stoppered tightly. All muscle studies were carried out in 2 separate aliquots and duplicate readings for each aliquot were obtained.

In order to determine the dry weight of the tissues, 2 of the tubes were placed in a drying oven at 105° C., left overnight, reweighed, and again dried until a constant weight was obtained. To determine fat content, the dry solids remaining were ground in a mortar, returned to the test tube, heated in an oven from 2 to 3 hours, and weighed. Five cubic centimeters of ethyl ether were added to the test tubes, the tubes swirled and allowed to stand for 10 minutes. The tubes were then centrifuged for 5 minutes at 1400 r.p.m. and the ether was removed with a capillary pipette. The procedure was repeated once with ethyl ether and then 4 times with petroleum ether. The tubes were dried in the oven, cooled and then weighed again.

The sodium and potassium contents of the tissues were determined according to the method of Farago *et al.*, utilizing nitric acid digestion of the tissue[14].

Results. Although results of tissue electrolyte studies obtained with somewhat different techniques from animals kept under somewhat varying dietary conditions may be difficult to compare, the following general statements may be made: our control skeletal potassium determinations (Group I and Group IV) agreed with those obtained by other investigators. Our control skeletal sodium determinations, on the other hand, are slightly higher[15,19]. The order of magnitude of these differences can be demonstrated best by the ratio of potassium to sodium. Calculated from our figures for fat free wet muscle tissue of dogs, this ratio was 1.7; the ratio calculated from the data of Ferrebee *et al.*[15] for fat free wet muscle was 2.2. This is a rather minor difference indeed, if the different techniques are considered by which these results were obtained. The control values for cardiac muscle potassium and sodium (Table 3) conform in general to those observed in literature[7,10,11,24,25,30,32]. The relatively wide range of control muscle potassium and sodium among the individual animals is similar to that noted by other investigators.

The effects of DOCA plus sodium chloride, DOCA plus potassium chloride and lanatoside C administration upon skeletal or cardiac muscle potassium and sodium content are noted in Tables 1 to 4 and may be summarized as follows: DOCA plus sodium chloride administration produced a significant decrease of plasma potassium and a slight increase of plasma sodium (Table 1). It further produced a significant decrease of skeletal muscle potassium and a significant increase of skeletal muscle sodium (Tables 2 and 3). While changes in similar direction seem to occur in the heart (right and left ventricle) they appear to be insignificant when compared with those of the skeletal muscle. Potassium chloride, when given simultaneously with DOCA prevented a significant decrease in the plasma and skeletal muscle potassium. Lanatoside C had no effect upon sodium and potassium content of the myocardium in normal dogs (comparison of Group I in Table 3 and Table 4). In most potassium deficient animals (Group II in Table 2) this glycoside, however, produced a signifi-

cant decrease of the sodium content of the skeletal muscle.

The mean lethal dose of lanatoside C was significantly less in the potassium depleted dogs (Group II) than in the control dogs (Group I): ($p<.05$). The mean of the lethal doses of all the 5 dogs of Group III which were treated with DOCA plus potassium chloride was just in between the mean of the lethal doses of the control dogs of Group I and the lethal doses of the potassium deficient dogs (Group II).

TABLE 2.—VALUES FOR MUSCLE SAMPLES IN MEQ./KG. FAT FREE DRY TISSUE

Dog	*Skeletal Muscle K Control*	*Skeletal Muscle K after DOCA*	*Skeletal Muscle K after Lanatoside C*	*Skeletal Muscle Na Control*	*Skeletal Muscle Na after DOCA*	*Skeletal Muscle Na after Lanatoside C*	*Lethal Dose Lanatoside C mg./kg.*
			Group I: Control Dogs				
7	403		371	214		121	0.32
9	250		364	180		115	0.31
12	375		376	258		137	0.24
13	248		327	220		164	0.37
17	285		237	165		114	0.32
18	268		398	175		137	0.26
22	390		381	286		149	0.34
26	356		397	155		163	0.26
27	309		334	191		144	0.29
Mean	320		354	206		138	0.30
			Group II: Dogs Receiving DOCA plus NaCl				
2		257	259		311	221	0.28
3		242	332		336	150	0.21
4		179	309		232	150	0.23
5		123	249			196	0.20
6		204	268		386	340	0.26
14		242	210		276	291	0.27
15		168	227		310	297	0.27
21		267	349		212	265	0.31
24		274	352		281	197	0.29
25		236	382		212	319	0.32
Mean		219	294		284	243	0.26
			Group III: Dogs Receiving DOCA plus KCl				
10		262	262		225	134	0.25
11		219	340		246	187	0.25
19		279	330		281	282	0.30
23		454	444			216	0.32
28		334	355		175	213	0.31
Mean		310	346		232	206	0.29

Discussion. The effects of DOCA on muscle and plasma electrolytes have been studied previously[11,12,15,17,19]. Our results further confirm those obtained by other investigators, who found a loss of potassium and a retention of sodium, at least during the first 10 days to 2 weeks of DOCA administration.

The significantly decreased lethal dose of lanatoside C which occurred in potassium depleted dogs subsequent to DOCA plus sodium chloride treatment did not show any statistically significant correlation to the decrease of plasma potassium or the increase of plasma sodium observed. This lack of correlation between plasma potassium and the lethal dose of the glycoside is

TABLE 3.—VALUES FOR MUSCLE SAMPLE IN MEQ./KG. FAT FREE DRY WEIGHT

Dog	*Right Ventricular K*	*Left Ventricular K*	*Right Ventricular Na*	*Left Ventricular Na*	*Lethal Dose Lanatoside C mg./kg.*
		Group I: Control Dogs			
7	266	304	153	163	0.32
9	271	287		159	0.31
12	390	335	230	255	0.24
13	366	335	247	215	0.37
17	325	312	187	219	0.32
18	359	347	163	169	0.26
22	371	280	243	224	0.36
26	305	296	200	218	0.26
27	311	263	213	237	0.29
Mean	329	306	204	206	0.30
		Group II: Dogs Receiving DOCA plus NaCl			
2	349	318	238	221	0.28
3	257	255	182	252	0.21
4	235	284	315	291	0.23
5	289		222	205	0.20
6	338	246	279	233	0.26
14	337	307	281	285	0.27
15	280	292	418	266	0.27
21	289	310	312	276	0.31
24	368	343	255	248	0.29
25	292	276	272	212	0.32
Mean	303	289	277	249	0.26
		Group III: Dogs Receiving DOCA plus KCl			
10	240		219	207	0.25
11	276	269	253	243	0.25
19	311	279	213	220	0.30
23	321	253	279	175	0.32
28	369	327	217	195	0.31
Mean	303	282	236	208	0.29

TABLE 4.—NORMAL DOGS KILLED BY AIR INJECTION. VALUES IN MEQ./KG. FAT FREE DRY TISSUE

Dog	*Skeletal Muscle K*	*Skeletal Muscle Na*	*Right Ventricular K*	*Left Ventricular K*	*Right Ventricular Na*	*Left Ventricular Na*
1) Control	440	199				
after death	395	168	320	322	234	271
2) Control						
after death	318	202	328	269	224	180
3) Control	399	103				
after death	437	111	321	329	244	228
4) Control	355	205				
after death	427	155	327	330	238	194
Mean						
Control	398	169				
after death	394	159	324	312	235	218

not surprising since the plasma potassium represents only a small fraction of the total body potassium.

The results are in general agreement with studies of Lown *et al.*[22] who found normal serum potassium levels in patients who developed increased sensitivity to digitalis as a result of induced potassium loss. Our findings agree also with those of Sampson *et al.*[27] who found that the beneficial effect of orally administered potassium upon ectopic rhythms due to digitalis toxicity persisted even after the serum potassium had returned to control levels.

There was a significant degree of correlation ($p>.05$) between the potassium content of the skeletal muscle at the time the infusion of lanatoside C was started, and the lethal dose of the glycoside in the potassium depleted dogs of Group II (Fig. 1). The mean of the lethal doses of the dogs of Group III in which depletion of muscle potassium was prevented by the combined administration of DOCA and potassium chloride was almost identical with the mean of the lethal doses of the control Group I. The 4 dogs (#4, 5, 6, and 15) with the lowest muscle potassium levels manifested definitely increased sensitivity to lanatoside C. Dog 6 further showed this increased response to the glycoside despite a normal plasma potassium level. The relatively low lethal glycoside doses in 2 control dogs (#12 and 26) which had rather normal muscle potassium values demonstrated that the potassium content of the tissues is not the

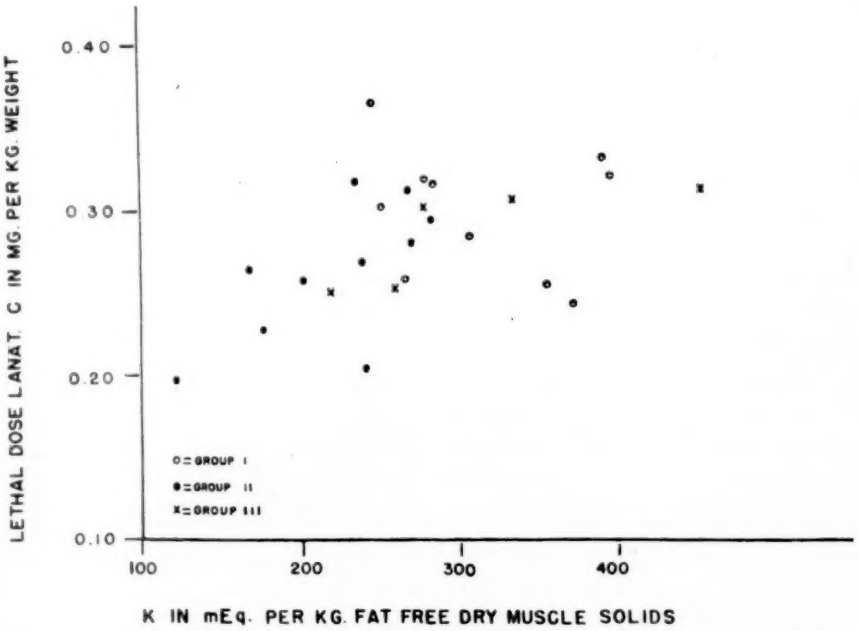

Fig. 1.—Scattergraph demonstrating the relationship of the lethal dose of lanatoside C to the skeletal muscle potassium content prior to the administration of lanatoside C. No correlation is present in Groups I and III. The Group II dogs show a significant degree of correlation.

only factor determining the effect of the glycoside.

The sodium content of the skeletal muscle before lanatoside C did not correlate significantly with the lethal dose of the drug in any group of animals studied.

The data presented seem to indicate that the increased response to lanatoside C is related to the depletion of tissue potassium. Direct evidence for the existence of a depletion of potassium in the myocardium as the ultimate cause of the increased response to the glycoside could not be ascertained by our experiments.

There was no significant difference in the mean potassium content of the ventricular myocardium of the normal dogs of Group I killed with lanatoside C and that of the 4 normal dogs killed by air injection. We were unable to confirm previous reports of potassium depletion in the myocardium following toxic or lethal doses of digitalis[1,4,7,16,18,29,31]. We did observe a significant increase in skeletal muscle potassium after lethal doses of lanatoside C in the potassium depleted dogs of Group II, but not in the other 2 groups.

Summary and Conclusions. The lethal dose of a standard solution of lanatoside C administered at a constant rate was determined in 3 groups of dogs under light anesthesia as follows: Group I: 9 normal control dogs; Group II: 10 dogs given daily injections of DOCA and drinking water containing sodium chloride in order to produce potassium depletion; Group III: 5 dogs given daily injections of DOCA with potassium chloride added to their drinking water in order to prevent the potassium depleting effect of the DOCA. An additional 4 normal dogs under light anesthesia were killed by air injection to serve as controls for the determination of the effect of lanatoside C on the potassium content of the heart and skeletal muscle. Control plasma and skeletal muscle sodium and potassium values were obtained in all the animals. Similar determinations were obtained after the administration of DOCA in Groups II and III. Sodium and potassium values for skeletal and cardiac muscle were obtained after death in the animals of all three groups.

The potassium depleted dogs showed a definitely increased sensitivity to lanatoside C when compared to the control animals as manifested by a lowered mean lethal dose.

In the potassium depleted animal the lethal dose of lanatoside C was found to be well correlated with the skeletal muscle, but not with the serum potassium level. Because the plasma potassium represents such a small part of the total body potassium, significant changes in intracellular and total body potassium levels may not be reflected by the plasma potassium concentration.

Skeletal muscle potassium increased after lethal doses of lanatoside C in potassium depleted dogs, but not in the control animals. However, no significant change in the potassium content of cardiac muscle was noted after lethal doses of lanatoside C. This is contrary to the findings of others who noted decreases in cardiac muscle potassium after toxic or fatal doses of digitalis preparations.

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LONG TERM TREATMENT OF RHEUMATOID ARTHRITIS WITH PARA-AMINOBENZOIC ACID AND CORTISONE ACETATE*

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In previous publications[14,15], we have reported on the synergistic action of para-aminobenzoic acid and cortisone acetate in the treatment of rheumatoid arthritis when the para-aminobenzoic acid is administered orally and the cortisone acetate given intramuscularly. These findings have been confirmed by others[6,10,18]. Our present report concerns itself with the combined oral administration of cortisone acetate and the sodium or potassium salt of para-aminobenzoic acid** in patients with rheumatoid arthritis who have been treated for one year or more.

Method and Materials. The patients reported here are all well substantiated cases of rheumatoid arthritis from the arthritis clinic of The Brooklyn Hospital and from the private practice of one of us (L.L.W.). For purposes of comparison the majority of these patients were first placed on the cortisone regime originally recommended by Hench *et al*[4] for a period of one to two weeks and then the dose of cortisone acetate was reduced to 37.5 mg. given orally in 3 divided doses of 12.5 mg. each spaced equally through the waking portion of the day. On this dose of cortisone acetate prompt relapse occurred in all our patients within a matter of days. As soon as relapse became manifest 30 cc. of a 10% solution of sodium or potassium para-aminobenzoate in water was administered exactly one hour prior to each dose of cortisone acetate. In those patients whose response appeared to be too slow or inadequate the quantity of sodium or potassium para-aminobenzoate solution was increased to 45 cc. of 10% solution per dose. At intervals control periods were instituted by withdrawing the para-aminobenzoic acid until the signs and symptoms of rheumatoid arthritis increased in severity. Similarly cortisone acetate was withdrawn while para-aminobenzoic acid administration was continued.

Each patient was seen and examined by one of us at intervals of one to two weeks and careful record made of the subjective response, objective manifestations of rheumatoid activity and of evidence of hypercorticoidism and of reactions to para-aminobenzoic acid. Our patients were classified according to the standards of the American Rheumatism Association[13] and by a simple method employed in our clinic in which activity of the rheumatoid process is graded one to 4 plus and response to therapy is estimated on a percentage basis giving equal weight to the patients subjective complaints and to objective evidence of rheumatoid activity. This additional method of evaluation of therapeutic response has in our opinion proved to be a highly sensitive indicator of improvement and of relapse. It possesses the virtue of permitting the indication of complete or nearly complete relief of pain and stiffness without requiring evidence of cure of the underlying cause of rheumatoid arthritis. Since no claim of cure is being made or implied we are using both these methods of evaluation.

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**The sodium and potassium para-aminobenzoate used in this study were provided through the courtesy of Dr. W. R. Bond, Director of Clinical Research, of the A. H. Robins Co.

Results. The results obtained by this method of treatment are summarized in Table 1. A total of 31 patients were treated by this method for periods of one year or more. Twenty-three of these patients received large doses of cortisone acetate for a period of one or two weeks before receiving combined oral cortisone acetate and sodium or potassium para-aminobenzoate by the method here described. In 22 of these 23 patients the improvement obtained by either method was quite comparable but in one patient improvement was far greater on large doses of cortisone alone. It is of more than passing interest that this patient insists on receiving sodium para-aminobenzoate but requires 75 mg. of cortisone acetate daily in order to maintain relief of arthritic manifestations equivalent to that obtained on 150 mg. of cortisone acetate alone. Eight patients were started on our regime without receiving large doses of cortisone at any time and their improvement has been quite satisfactory. Aside from weight gain which did not produce weight in excess of normal age-height-weight standards and rare mild rounding of the face we have not encountered any of the well known stigmata of hypercorticoidism. Two of these patients developed a toxic drug rash due to the para-aminobenzoic acid after 12 and 13 months of therapy respectively. In these 2 patients this therapy had to be discontinued. In each case drug allergy developed when the drug was re-instituted after a control period. The only other complaints referable to the sodium or potassium para-aminobenzoate in this group of patients were some objection to the briny taste of the solution which could be overcome by the addition of flavoring and the occasional complaint of heartburn

TABLE 1.—DESCRIPTION AND RESPONSE TO THERAPY OF CASES OF RHEUMATOID ARTHRITIS

Name	*Age*	*Sex*	*Duration Arthritis (years)*	*Severity of Arthritis*	*Response Standard Doses Cortisone*	*Response Cortisone and PABA*	*Duration Cortisone and PABA*	*American Rheumat. Assn. Classification*		
								Anat.	*Funct.*	*Therap.*
L. W.	42	M	12	3 plus	90%	90%	3¼	ii	ii	ii
J. V.	35	F	4½	3 plus	90%	90%	2½	ii	ii	ii
A. C.	35	M	14	4 plus	90%	80%	2½	iv	iii	ii
R. B.	42	F	20	3 plus	100%	90%	2¼	iii	iii	ii
C. G.	28	F	12	4 plus	90%	90%	2	iv	iii	ii
D. R.	32	F	14	4 plus	80%	90%	2½	iv	iv	ii
V. C.	34	F	1	3 plus		80%	1½	ii	ii	ii
F. E.	56	M	7	3 plus	—	100%	2½	i	iii	i
O. L.	57	F	4	3 plus	90%	90%	2	iii	ii	ii
E. L.	62	F	8	3 plus	—	95%	1½	iii	ii	ii
B. R.	47	F	11	3 plus	90%	80%	2 1/12	iii	iii	ii
H. B.	52	F	9	3 plus	100%	100%	1½	ii	iii	i
M. F.	50	M	14	4 plus	—	75%	1½	iv	iii	ii
A. G.	48	F	2	4 plus	—	90%	1 7/12	iii	iv	ii
A. C.	65	F	20	2 plus	95%	90%	1¼	ii	ii	i
M. M.	59	F	23	3 plus	—	80%	1¼	ii	ii	ii
D. P.	64	F	22	4 plus	80%	40%	1¼	iii	iv	ii
E. R.	28	F	9	3 plus	90%	90%	1 1/12*	iii	iii	ii
E. D.	51	F	2	2 plus	—	100%	1	ii	ii	ii
M. F.	39	F	2	3 plus	90%	80%	2½	ii	ii	ii
M. A.	70	F	2	3 plus	90%	90%	2	ii	iii	ii
R. I.	27	F	1	4 plus	90%	100%	2	ii	iv	ii
H. C.	49	F	5	4 plus	100%	90%	1½	iii	iv	ii
S. G.	37	F	4	4 plus	100%	80%	2	iii	iv	ii
G. S.	43	F	16	3 plus	100% †	80%	1	iii	iii	ii
E. P.	65	F	6	4 plus	80%	80%	1	ii	iii	ii
A. N.	65	F	25	2 plus	—	100%	1	ii	ii	ii
F. C.	48	F	18	2 plus	100%	100%	1*	i	ii	i
D. M.	38	M	3	3 plus	100%	90%	1	i	iii	ii
A. R.	41	F	7	4 plus	90%	90%	1	ii	iii	ii
L. P.	28	F	2	2 plus	100%	100%	1	i	ii	ii

* These patients developed toxic drug rash due to PABA.
† This patient could not tolerate standard doses of cortisone for more than one week.

which was easily controlled by the administration of whole milk.

The rate of improvement of patients on this form of therapy has been different from that obtained on conventional dose cortisone therapy. The euphoria which is so prominent on large doses of cortisone has not been noted in any of our patients. In severe cases improvement has been gradual and often maximal improvement has not been reached until therapy has been continued for as long as 60 to 90 days. This slow rate of improvement by the method here described has been speeded in other patients not included in this study in whom the interval between large dose cortisone therapy and the addition of para-aminobenzoic acid to small doses of cortisone has been omitted.

Conversely we have not had to interrupt treatment in any of our patients because of evidence of hypercorticoidism or because of the development of intercurrent infections, peptic ulcer, psychosis and the like. The purpose of our study has been the long continued suboptimal suppression of the manifestations of rheumatoid arthritis with a daily dose of cortisone acetate of 37.5 mg. Larger doses of cortisone acetate combined with para-aminobenzoic acid can and have been used but are not a part of this study.

The following case reports will serve to illustrate the response to combined treatment with cortisone acetate and sodium or potassium para-aminobenzoate:

Case Reports. CASE No. 1: S.G., a 37-year-old white spinster, developed rheumatoid arthritis in 1947, with onset of moderate severity but with a rapid and relentless downward course. She became completely disabled and almost totally bedridden by January, 1950. In June, 1950, she was hospitalized and received intramuscular cortisone acetate with an average daily dose of 200 mg. for 60 days with marked but not complete subjective and objective improvement. From September, 1950, until January, 1951, she received a daily intramuscular dose of 50 mg. of cortisone acetate with marked increase in the subjective and objective manifestations of her disease. Between January and April, 1951, this relapse became exceedingly severe and the patient again became a total invalid, unable to care for herself.

When first seen by one of us (L.L.W.) in April, 1951, the patient was totally disabled and could not care for her simplest wants. She was hospitalized and in order to evaluate any possible adrenal atrophy was given 100 mg. of ACTH daily for 10 days with rapid production of eosinopenia and with moderate improvement manifested by lessening of pain, but in spite of this, she was still unable to care for herself or to walk. At this time there was evidence of marked rheumatoid activity in both feet, ankles, knees, both hands, elbows and shoulders. There was roentgenographic evidence of marked bony destruction of both ankle and wrist joints and there was fibrous fixation of both wrists and elbows.

After the initial course of ACTH she was given 30 cc. of sodium para-aminobenzoate solution followed in one hour by 12.5 mg. of cortisone acetate this being repeated three times daily. She improved slowly on this dosage until by May 10, 1951, she was able to walk, wear shoes and care for herself. This medication was continued until October 27, 1951, at which time she had achieved between 80 and 90% relief of symptoms. Sodium para-aminobenzoate was discontinued at this time for purposes of control and daily dose of 50 mg. of cortisone acetate in 4 divided doses given. After 3 weeks on this regime she developed increasing pain and swelling in several joints and sodium para-aminobenzoate was again given. From December 8, 1951 to August 14, 1952, she was maintained on 45 cc. of sodium para-aminobenzoate solution and 12.5 mg. of cortisone acetate administered 3 times daily in the usual manner with relief estimated at 80%. Early in 1952, she sought and obtained employment as a file clerk and typist and has been steadily employed at this occupation since then. In August, 1952, sodium para-aminobenzoate was again withdrawn and relapse became manifest after an interval of 6 weeks. Combined therapy was again instituted and has been employed steadily since that time. The patient has pain and some swelling in single joints on occasion, usually after an upper respiratory infection but has

been able to continue at her employment without loss of time.

CASE NO. 2: F.E., a 56-year-old colored male, developed rheumatoid arthritis in 1943, which became so severe that he abandoned work as a shipfitter. He received gold therapy elsewhere with good response for 2 years but then became gradually worse. When first seen by us in January 1951, he was totally disabled and on home relief. He had marked involvement of both hands precluding their use other than for personal care and moderately severe involvement of both elbows and knees. He was given 2 gm. of sodium para-aminobenzoate followed by 12.5 mg. of cortisone after an interval of one hour, 3 times daily. Within 2 weeks he experienced complete relief of pain and swelling and exhibited only residual stiffness of the fingers. Medication was continued until June 6, 1951, when the sodium para-aminobenzoate was discontinued. For 12 weeks he remained well but then relapsed severely. On September 26, 1951, sodium para-aminobenzoate was resumed. Thirty cubic centimeters of sodium para-aminobenzoate solution was given one hour before each dose of 12.5 mg. of cortisone for a total of 3 such doses daily. On October 10, 1951, relief of pain and swelling was complete and within a few weeks even stiffness had disappeared. From December 26, 1951 to January 23, 1952, the sodium para-aminobenzoate was withheld while the cortisone acetate was continued and relief was maintained. From January 23, 1952 to March 12, 1952, the patient abandoned all treatment and developed a severe exacerbation. From March 12, 1952 to May 7, 1952, he was given 37.5 mg. of cortisone acetate daily without relief. On May 12, 1952, 30 cc. of sodium para-aminobenzoate solution was added to the cortisone by the usual method and the patient manifested rapid relief. Combined therapy was continued until October 12, 1952, when the sodium para-aminobenzoate was discontinued. He has remained asymptomatic since then on 37.5 mg. of cortisone acetate daily without recurrence. The patient has been gainfully employed since June, 1952.

CASE NO. 3: H.C., a 49-year-old married white female, first developed rheumatoid arthritis in 1946 with gradual onset pain, swelling and stiffness of both hands, wrists, elbows, shoulders, knees and ankles. With the aid of salicylates she was able to continue to work in spite of pain until December, 1950, when following a respiratory infection she became totally disabled. In January, 1951, she was given intramuscular cortisone by her family physician and received a daily dose of 100 mg. until June, 1951. During this period she was fairly well controlled and was able to care for herself with only moderate pain but could not walk more than half a block. In June, 1951, she began to develop increasing pain and swelling in spite of continued treatment and became so discouraged that she discontinued treatment.

When first seen by us she was very much depressed and showed marked involvement of both hands, wrists, shoulders, knees, ankles and feet. At this time she was unable to care for her simplest wants. Since she was quite disabled she was hospitalized. She received full doses of cortisone acetate intramuscularly and obtained complete subjective relief of pain and obtained major objective improvement of swelling, heat and joint tenderness. After 2 weeks of this treatment the dose of cortisone was reduced to 12.5 mg. given orally 3 times daily with 30 cc. of 10% solution of sodium para-aminobenzoate preceding each dose of cortisone acetate by one hour. On this regime she relapsed partially until relief of rheumatoid manifestations was estimated at only 80% at the end of one week. This regime was continued until on February 25, 1952, relief of arthritic manifestations had reached 100%. This relief was maintained until June 17, 1952, at which time the sodium para-aminobenzoate was withdrawn for control purposes. Partial relapse became manifest 2 weeks after the control period had been initiated and full relapse was evident 69 days after initiation of control on a daily dose of 37.5 mg. of cortisone acetate. On October 8, 1952, the sodium para-aminobenzoate was re-instituted and the patient improved rapidly. Since that time she has been able to maintain complete relief of the manifestations of rheumatoid arthritis on this treatment. She has been continuously employed at her usual occupation as a clerk since October, 1951.

Discussion. We have purposely limited this report to a group of patients who have been treated by this method for one year or more because the course of rheumatoid arthritis is quite unpredictable and prone to spontaneous remissions. As nearly as is possible we have tried to exclude the influence of spontaneous remissions by

instituting control periods up to the point of at least partial relapse at frequent intervals.

That para-aminobenzoic acid and cortisone act synergistically has been shown by a number of clinical studies[6,10,14,15,18]. Para-aminobenzoic acid alone in doses up to 24 gm. per day for 4 weeks failed to produce significant clinical improvement in rheumatoid arthritis[18]. In the doses we have employed, para-aminobenzoic acid alone has failed to suppress the manifestations of rheumatoid arthritis. The mechanism of synergistic action of cortisone and para-aminobenzoic acid is under investigation.

Our original theory was based on the known interference of para-aminobenzoic acid with the inactivation of female sex hormone by liver tissue. Our premise that cortisone must follow a similar metabolic pathway in the body has since been substantiated by the experimental results of others[7,12]. We have been able to demonstrate by *in vitro* experiment that the known destruction of cortisone by liver tissue is markedly inhibited by the addition of para-aminobenzoic acid to the substrate[16]. The mechanism of this interference can only be inferred at this time. We have previously demonstrated that tetraethylthiuram disulphide acts synergistically with cortisone in much the same manner as does para-aminobenzoic acid[17]. Tetraethylthiuram disulphide is known to interfere with various oxidative enzymes and with oxygen consumption by the liver[5,11]. Tetraethylthiuram disulphide may act as a competitive hydrogen ion acceptor[9]. Therefore it is quite possible that para-aminobenzoic acid acts by inactivating hepatic oxidative enzymes or by competing with cortisone for these enzymes or one or more of the co-enzymes. Further investigation of the intermediate steps of this reaction is in progress.

We wish to emphasize the fact that we have been able to maintain patients with rheumatoid arthritis on sodium or potassium para-aminobenzoate and cortisone acetate for periods up to 3 years without encountering any of the dire side effects observed by others with the usual doses of cortisone[8], and with satisfactory sub-optimal suppression of the symptoms and signs of rheumatoid arthritis. We have not encountered glycosuria, hypertension, psychosis, hirsutism, obesity, striae, tuberculosis, periarteritis nodosa or any other serious side reaction. The only difficulty we have observed has been a tendency for upper respiratory infections to persist longer than usual in patients on this therapy. Exacerbations of rheumatoid activity following upper respiratory infections have been fairly common. These exacerbations have yielded to continued treatment in all cases studied.

To date the combination of para-aminobenzoic acid and cortisone in the doses employed has proved to be a useful method for the clinical suppression of rheumatoid arthritis with the advantage of relative safety and the ability to maintain therapy for long periods without the development of refractoriness, side reactions or serious complications. It should be emphasized that for the purpose of investigation we have limited ourselves to a dose of cortisone acetate so small that in itself it has proved completely ineffective in overcoming rheumatoid manifestations in the cases studied. Larger doses can be used and have been employed with para-aminobenzoic acid in the suppression of the manifestations of the various collagen system diseases. In general it has been our impression that the addition of

para-aminobenzoic acid increases the anti-inflammatory or antiphlogistic action of a given dose of cortisone acetate two to threefold. This potentiation has not been accompanied by a similar increase in the incidence of "side reactions." Studies directed at an explanation of this apparent paradox are now under way.

Summary and Conclusions. 1. Thirty-one patients with active rheumatoid arthritis were treated with a combination of para-aminobenzoic acid and cortisone for a period of one year or more.

2. Thirty of these patients showed improvement comparable to that obtained with a much larger dose of cortisone acetate administered alone.

3. The incidence of evidence of hypercorticoidism was negligible. Other known complications of cortisone therapy were absent.

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EFFECT OF PARA-AMINOBENZOIC ACID ON THE METABOLISM OF CORTISONE IN LIVER TISSUE*

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In previous reports we have presented clinical evidence of the synergistic action of para-aminobenzoic acid and cortisone in the treatment of rheumatoid arthritis[6,7,8]. These clinical studies have been confirmed by others[2,4,10]. Our original hypothesis was based on the known interference of para-aminobenzoic acid with the inactivation of female sex hormone by liver tissue *in vitro*[1]. The similarity in structure of cortisone and female sex hormone suggested to us that both might pursue a similar metabolic pathway in the body. Since at that time nothing was known of the inactivation of cortisone in the body we resorted to clinical trial. The results which were obtained were sufficiently encouraging to warrant the use of this method for continued treatment of rheumatoid arthritis.

Since then convincing proof of the inactivation of cortisone largely by liver tissue has been produced[3,5]. We have adapted the method of Schneider and Horstmann[5] to test the synergistic action of para-aminobenzoic acid and cortisone *in vitro*.

Method. We have followed the procedure outlined by Schneider and Horstmann** and have modified it only by adding sodium para-aminobenzoate to the test vessels prior to incubation. Sodium para-aminobenzoate was used in concentrations ranging from 5 to 50 mg. per test vessel. Suitable controls in accordance with the original method were employed. After incubation our procedure followed the protein precipitation and extraction procedures and column chromatography of the original method without deviation. Two analytic procedures were employed namely ultraviolet spectrophotometry over the range of 220 to 260 mu and the Porter-Silber assay.

Results. A total of 31 satisfactory experiments were performed with the above method. An illustrative experiment employing rat liver slices is reported in Table 1. A similar experiment employing surviving human liver slices is shown in Table 2. Only ultraviolet spectroscopic results obtained are reported since we found that side chain destruction was too marked to give measurable results with the Porter-Silber reaction.

As these experiments illustrate, almost complete destruction of cortisone acetate occurred in the control vessels which did not contain sodium para-aminobenzoate while very marked preservation of the conjugated unsaturated system of the cortisone molecule was present in the vessels containing sodium para-aminobenzoate. Thus 86.9% of the cortisone present was reduced by rat liver slices after 3 hours of in-

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cubation while in the presence of from 5 to 50 mg. of sodium para-aminobenzoate per vessel only 22.7% was so reduced. Using surviving human liver slices 82.7% of the cortisone is degraded after 3 hours of incubation while in the presence of similar quantities of sodium para-aminobenzoate 17.4% of cortisone was destroyed. Quantities of sodium para-aminobenzoate less than 5 mg. per vessel were not effective in inhibiting cortisone degradation to a significant degree. All experiments performed produced very similar results.

Discussion. These experiments confirm the findings of other investigators that Compound E is rapidly metabolized by liver tissue under the conditions experimentally imposed. This metabolic degradation is markedly interfered with when para-aminobenzoic acid or its salts are added to the system. The para-aminobenzoic acid appears to inhibit the degradation of the conjugated unsaturated system of the Compound E molecule far more than the degradation of the side chain.

TABLE 1.—INCUBATION OF COMPOUND E AND PABA WITH RAT LIVER SLICES

	Ultraviolet Spectroscopy		
Vessel No.	*At 240 mu.* D	*Average* D	*Per Cent Reduction*
1—(Bp)	0	0	
2—(Cp_1)	0.140		
3—(Cp_2)	0.134	0.137	
4—(E_1)	0.022		
5—(E_2)	0.014	0.018	86.9
6—(Ep_1)	0.110		
7—(Ep_2)	0.102	0.106	22.7

Blank vessel (Bp) contained 15 mg. of PABA and 210 ± 2 mg. of rat liver slices in buffered solution. Control vessels (Cp_1 and Cp_2) contained in addition 840 gamma of Compound E worked up without incubation. Vessels (E_1 and E_2) containing the measured amount of Compound E in the tissue buffered solution were incubated for 3 hours in an oxygen atmosphere. Vessels (Ep_1 and Ep_2) contained in addition to the measured amount of tissue and Cortisone 15 mg. of PABA in buffered solution. These vessels were treated in the same manner as vessels (E_1 and E_2).

TABLE 2.—INCUBATION OF COMPOUND E AND PABA WITH HUMAN LIVER SLICES

	Ultraviolet Spectroscopy		
Vessel No.	*At 240 mu.* D	*Average* D	*Per Cent Reduction*
1—(Bp)	0	0	
2—(Cp_1)	0.130		
3—(Cp_2)	0.125	0.127	
4—(E_1)	0.025		
5—(E_2)	0.020	0.022	82.7
6—(Ep_1)	0.110		
7—(Ep_2)	0.100	0.105	17.4

Experiment outlined in this table was identical with the one shown in Table 1 except that in this run human liver slices were substituted for those of the rat.

One can only speculate at this time as to the exact nature of the enzymatic systems involved. Indirect clinical evidence employing tetraethylthiuram disulphide[9] would tend to support the impression that several known hepatic oxidative enzymes are blocked. Tetraethylthiuram disulphide does not lend itself to *in vitro* experiment because of its marked insolubility in physiologic fluids but clinically has been shown to exert a similar synergistic action with cortisone when administered to patients with rheumatoid arthritis. Further attempts to investigate the metabolic pathways involved in the degradation of cortisone are now in progress.

The experimental *in vitro* findings above reported are proof of the validity of our original hypothesis and serve to support and explain our clinical results with combined cortisone and para-aminobenzoic acid therapy of rheumatoid arthritis.

Summary. 1. The metabolism of cortisone in surviving rat and human liver slices has been studied and previously reported findings have been confirmed.

2. Para-aminobenzoic acid has been shown to interfere markedly with the rapid reduction of the unsaturated conjugated system of the cortisone molecule while permitting more rapid degradation of the side chain.

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OBSERVATIONS ON THE DIURETIC RESPONSE TO PAREPHYLLIN (R-3588),* NEOHYDRIN** AND MERCUHYDRIN WHEN ADMINISTERED ALONE AND IN COMBINATION†

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Many drugs have been used in combination with mercurial diuretics in an attempt, by additive or possibly synergistic means, to augment the effect of the mercurial compound. Among the drugs used for this purpose, the xanthine derivatives have been widely tested. The combined use of these agents followed the observations of Herrmann, Stone and Schwab[7], who, in 1932, reported that the simultaneous or proper sequential administration of aminophylline, given orally or intravenously together with intravenous Salyrgan, greatly exceeded the diuretic response that was obtained when the mercurial was used alone. Subsequent observers[4,10,11,12] have stressed that in using xanthine compounds in combination with mercurial diuretics, the dosage of each drug used, their route of administration and the time sequence in which they were given were all of significance. Aminophylline must be given in large doses to be effective; therefore, it must be given parenterally, since doses adequate to be effective are poorly tolerated by the oral route and almost routinely give rise to gastric irritation. With this in mind, clinical investigation was undertaken with Parephyllin (diethyl-aminoethyl-theophylline hydrochloride) (Riker-3588), a 7-substituted theophylline derivative. Due to its prompt solubility at neutrality and its stability throughout a wide biological pH range, this drug offered the probability of being readily tolerated when administered by both the parenteral and the oral route. Initial observations were made on the effect of Parephyllin on water and electrolyte excretion in normal control subjects (Group 1) using the parenteral route of administration. The remainder of the studies were carried out on patients in heart failure. The observations on the patients with cardiac failure consisted of evaluating the diuretic effect of Parephyllin given alone (orally) and in combination (orally and parenterally) with Mercuhydrin given parenterally and Neohydrin given orally. These results were then compared with the diuretic response to each of the

*Diethyl-aminoethyl theophylline hydrochloride supplied through the courtesy of Riker Laboratories, Inc., also known as Soluphylline.

**Neohydrin supplied through the courtesy of Lakeside Laboratories, Inc.

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mercurials given alone by the same route as when given in combination with the xanthine. Comparative observations were also made using aminophylline in place of Parephyllin.

Methods and Materials. This study was done in three parts: (1) the acute diuretic effect of parenterally administered Parephyllin (diethylaminoethyl theophylline hydrochloride) (R-3588) was first investigated in normal control subjects (Group 1). Six patients were used in this test; they were given 500 cc. of water initially, and then 250 cc. of water at hourly intervals for the duration of the study. Urine samples were collected at hourly intervals and their volumes recorded and sodium and potassium contents were determined by the Beckman analytical technique. The first three 60-minute periods, prior to drug administration, were used as the control observations. At the end of the control periods, and again one hour later, 0.5 gm. of Parephyllin was given intramuscularly. The urine was collected for four 60-minute periods after the drug was administered. The hourly urine volumes and sodium and potassium excretion rates before and after the administration of Parephyllin were then compared (Table 1).

(2) The second part of the study (Group 2) was an evaluation of additive or synergistic effects of Mercuhydrin and Parephyllin or aminophylline when administered parenterally. The effect of the drugs was studied in eight patients with cardiac disease who showed clinical evidence of varying degrees of congestive heart failure. After collecting the urine for a 24-hour control period, 2 cc. of Mercuhydrin were given intramuscularly and the urine was again collected for the following 24-hour period. This served as the response to the mercurial alone. After a rest period and a second 24-hour control period, 2 cc. of Mercuhydrin were again given intramuscularly along with Parephyllin intramuscularly, (0.5 gm. 4 times daily) to 4 patients; while in the remaining 4, the mercurial injection was followed by the administration of the Parephyllin intravenously (0.5 gm.). In 5 of these patients, following a rest period and a third control output study, aminophylline was given in an equivalent milligram dosage to the Parephyllin and by similar routes of administration, concomitant with the mercurial. Twenty-four hour urine volumes, and sodium and potassium excretion values were determined in all cases while the patients were under study. In this way, the diuretic effect of the combination of Parephyllin with Mercuhydrin could be compared to the effect of the mercurial alone and to that of the combination of the mercurial with aminophylline.

(3) The third phase of the investigation (Group 3) was an attempt to evaluate the therapeutic effect of a mercurial diuretic and Parephyllin alone and in combination, when the drugs were administered orally. The oral mercurial compound used was Neohydrin, (3-chloromercuri-2-methoxypropylurea). The response was then compared to that obtained with parenteral Mercuhydrin given in a dose containing the same amount of mercury as the oral mercurial. Seven patients (Group 3) with cardiac disease who showed overt evidence of congestive heart failure were used. In 3 patients after a 24-hour collection period which served as a control, the Neohydrin was given for 3 consecutive 24-hour periods in doses containing 20 mg. of mercury (2 tablets) 4 times daily. On the fifth, sixth and seventh days, Parephyllin was given in addition to the mercurial. The dosage varied from 0.6 to 1.0 gm. 4 times daily, depending on individual tolerance. Then, the mercurial was discontinued and for the succeeding 3 days, the Parephyllin was administered alone in the same dosage. In the other 4 patients studied, the drugs were likewise given for 3-day intervals, but in reverse order. First, the Parephyllin was given alone, then it was administered in combination with Neohydrin, and then the mercurial was given alone. Finally, after a rest period, 2 cc. of Mercuhydrin was given intramuscularly to all except one patient and the urine was collected for the succeeding 24 hours. This served as a comparison for the excretion values obtained during the period in which the patients were receiving oral medication. In each instance, the daily urine volume was measured, and the 24-hour excretion of sodium and potassium determined.

For further comparison, a combination of oral Neohydrin and oral aminophylline (the latter in doses of 540 mg. 4 times daily) was used in 4 patients. A similar sequence of drug administration was used, and again 24-hour determinations of urine volume and sodium and potassium excretion rates were recorded.

Results. PART I. DIURETIC EFFECT OF R-3558 ALONE. In the 6 normal control subjects who were given the drug intramuscularly the mean sodium excretion

rose from a control level (average of 3 consecutive 60-minute periods) of 3.4 mEq. per hour to 4.4 mEq. per hour during the first hour after the drug was given, then fell to mean values lower than the control level. Urine volume and potassium excretion values increased slightly (167 cc. to 231 cc. and 1.9 mEq. to 2.7 mEq., respectively) to maximum levels in the third hour of post-drug excretion (Table 1).

TABLE 1.—EFFECT OF INTRAMUSCULAR ADMINISTERED PAREPHYLLIN (R-3588)* ON WATER AND ELECTROLYTE EXCRETION IN NORMAL SUBJECTS

	Control period			*Period after drug administration*					
				1st hour			*2nd hour*		
Patien	*U.V. cc./hr.*	*Na excr. mEq./hr.*	*K excr. mEq./hr.*	*U.V. cc./hr.*	*Na excr. mEq./hr.*	*K excr. mEq./hr.*	*U.V. cc./hr.*	*Na excr. mEq./hr.*	*K excr. mEq./hr.*
C. T.	283	3.6	2.7	155	3.0	1.7	300	3.9	2.5
O. A.	343	4.4	3.;	235	3.0	4.3	285	3.6	5.3
T. N.	53	1.5	1.4	40	0.9	1.3	40	0.9	1.4
J. B.	257	4.9	2.1	365	8.1	2.3	130	6.4	3.0
T. R.	36	0.9	0.7	45	0.9	0.7	35	0.7	0.5
A.S.	32	4.9	1.1	55	10.3	2.0	10	1.6	0.3
Mean	167	3.4	1.9	149	4.4	2.1	133	2.9	2.2

	Period after drug administration								
	3rd hour			*4th hour*			*Average for 4-hour drug period*		
C. T.	635	2.4	2.7	370	1.3	1.6	365	2.7	2.1
O. A.	285	3.6	5.7	320	3.5	4.7	281	3.4	5.0
T. N.	50	1.3	1.6	38	1.0	1.2	42	1.0	1.4
J. B.	150	5.4	2.8	285	6.4	2.1	233	6.6	2.6
T. R.	35	0.7	0.5	25	0.4	0.3	35	0.7	0.5
A. S.	—	—	—	40	4.4	1.5	35	5.4	1.3
Mean	231	2.7	2.7	180	2.8	1.9	165	3.3	2.2

* Dose—1.0 gm.
U.V.—Urine Volume
Na excr.—Sodium excretion in urine
K excr.—Potassium excretion in urine

However, comparison of the mean hourly excretion values for the 6 patients during the control period (average of 3 one-hour periods) with the average mean hourly excretion values for the entire post-drug period showed no appreciable diuretic effect of the xanthine (Table 1). The intramuscular injections of the drug were well tolerated by all 6 patients.

PART II. DIURETIC EFFECT OF PAREPHYLLIN GIVEN INTRAMUSCULARLY AND INTRAVENOUSLY IN COMBINATION WITH INTRAMUSCULAR MERCUHYDRIN AND A COMPARISON WITH MERCUHYDRIN GIVEN ALONE (INTRAMUSCULAR) AND MERCUHYDRIN COMBINED WITH AMINOPHYLLINE (GIVEN INTRAVENOUSLY AND INTRAMUSCULARLY). Parephyllin given parenterally on the same day as the intramuscular injection of Mercuhydrin produced no greater percentage increment in 24-hour urine volume than did Mercuhydrin given alone, and than did a combination of Mercuhydrin with parenteral aminophylline (Table 2). Moreover, when Parephyllin was given intramuscularly to 4 patients there was actually a smaller increment in the total volume of urine and in electrolyte excretion over control levels than after Mercuhydrin alone or the combination of Mercuhydrin and aminophylline. Therefore, Parephyllin offered no advantage over aminophylline since it was ineffective as a diuretic by the intramuscular route. In fact the addition of either aminophylline or Parephyllin did not appear to increase the diuretic potency of Mercuhydrin.

In the patients in whom Parephyllin was given intravenously, too rapid administration of the drug produced com-

plaints of dizziness, lightheadedness, giddiness and nausea. When the injection was slow, requiring 7 to 10 minutes for injection of the entire 500 mg. these complaints were minimal. Again, the drug was well tolerated intramuscularly.

PART III. DIURETIC EFFECT OF ORAL PAREPHYLLIN, ALONE AND IN COMBINATION WITH NEOHYDRIN. Parephyllin when given alone orally in tolerated doses failed to show a consistent diuretic effect. The 7 patients studied showed a mean increment in urine volume of 20%, in sodium excretion of 22% and in potassium excretion of 32% (Table 3 and Fig. 3), all of which were inconstant responses. By contrast, when Neohydrin was given alone there was a consistent increase in sodium excretion amounting to an average increment of 496%. This compared to an increase of 586% after 2 cc. (equivalent to 80 mg. Hg) of Mercuhydrin. The effect of Neohydrin on water excretion was less consistent, probably a result of our inability to completely regulate the 24-hour intake. However, Mercuhydrin appeared to be more consistent and superior to oral Neohydrin in producing diuresis. The patients in the oral study who had received oral Neohydrin first, followed by the combination of Neohydrin and Parephyllin before they received the xanthine alone, showed a continued diuresis and natriuresis during the first day after the mercurial was discontinued which did not continue during the second and third day. This was thought to be due to the persistent effect of the Neohydrin and hence the volume and excretion values for the first day of Parephyllin alone were discarded from the study. In these 3 patients, only the second and third days were considered to be the effect of the Parephyllin alone.

TABLE 2.—DIURETIC EFFECT OF PARENTERAL MERCUHYDRIN (I. M.) ALONE AND IN COMBINATION WITH

Excretion

Group 2A	*First control period*			*Mercuhydrin alone I. M.*						*Second control period*			
					% inc.		% inc.		% inc				
Patient	*Urine*	*Na*	*K*	*Urine*	*U.V.*	*Na*	*Na*	*K*	*K*	*Urine*	*Na*	*K*	*Urine*
C. T.	4415	173.0	20.4	3325	−25	206.8	20	27.7	36	3315	144.2	48.4	3325
E. B.	520	5.9	21.0	1520	192	62.6	961	23.3	11	615	9.6	26.9	1820
R. H.	3550	44.8	8.2	4950	39	355.3	693	12.7	55	3660	55.7	15.4	3985
H. F.	1350	21.1	19.0	3980	195	190.1	801	36.5	92	1340	18.1	24.0	1745
Mean	2459	61.2	17.2	3444	100	203.7	619	25.1	49	2233	56.9	28.7	2719
Group 2B	*First control period*			*Mercuhydrin alone I. M.*						*Second control period*			
Patient													
W. B.	2300	81.0	40.0	1890	−18	155.4	92	52.7	32	2300	20.0	50.0	1985
O. A.	1450	17.7	51.7	2000	38	67.9	284	60.4	17	1000	18.3	58.6	2110
I. H.	750	40.4	41.5	2210	195	166.3	312	56.0	35	1550	56.0	57.5	3200
H. H.	535	6.3	4.9	860	61	27.3	333	9.2	88	400	4.5	7.2	675
Mean	1259	36.4	34.5	1740	69	104.2	255	44.6	43	1313	24.7	43.3	1993
Grand** Mean	1859	48.8	25.9	2592	85	154.0	437	34.9	46	1773	40.8	36.0	2356

Na—Sodium excretion in mEq./24 hours
Urine—Urine excretion in cc./24 hours
K—Potassium excretion in mEq./24 hours

The 4 patients in whom parallel studies with aminophylline (oral) and Neohydrin (oral) were done showed a similar phenomenon; the xanthine given first alone produced a slight but insignificant diuretic response, and when given during the final 72 hours of sequence was unable to sustain the diuresis which had been initiated by the combined administration of Neohydrin and aminophylline. Hence, this combined effect was thought to be primarily a reflection of the effect of the Neohydrin.

Discussion. The clinical problem of inducing and maintaining diuresis in patients in congestive heart failure has led many investigators to study the

efficacy of administering combinations of diuretic drugs. The therapeutic endpoint desired from such combinations was outlined by Herrmann *et al.*[6,11] and included: (1) the production of a diuresis greater than that which can be accomplished by the use of the 2 drugs separately; (2) the inducement of a response in instances where one drug alone in the same dosage had failed; and (3) the accomplishment of diuresis with smaller doses of the drugs in cases in whom either drug alone would be ineffectual. Since the introduction of the mercurial compounds and their recognition as diuretic agents, most combinations of drugs used for these purposes have included at least one mercurial compound.

Vogl and Esserman[12], in a recent survey of this problem, mention that with the use of mercurials alone, in patients who are adequately digitalized and whose serum electrolytes are maintained at normal levels, increased diuresis may be accomplished only by increasing the individual dose or the frequency of administration of the diuretic. However, this latter may increase the danger of mercurialism, which, these authors state, rises in inverse proportion to the diuretic effect since a considerable amount of mercury is retained if diuresis is insufficient. With the advent of additional compounds shown to exert a diuretic action, such as the acid-forming salts, urea, hypertonic glucose and the xanthine derivatives, the possibility of using them in combination with the mercurials for their additive, and perhaps synergistic effects arose. This possibility was greatly enhanced when further investigation suggested that these other compounds had mechanisms for producing diuresis which were different from that of the mercurials. The mechanism of xanthine diuresis has been the subject of considerable investigation. Crawford and McDaniel[1], in 1935, stated that a review of the literature to that date seemed to indicate that the xanthine and mercurial diuretics have their main actions on the kidney, the former increasing glomerular filtration and the latter retarding tubular reabsorption. In agreement with this, Escher *et al.*[3] found that in normal subjects, aminophylline produced a significant increase in cardiac output which parallelled an increase in glomerular filtration rate and renal plasma flow. However, the glomerular filtration rate remained ele-

INTRAVENOUSLY AND INTRAMUSCULARLY ADMINISTERED PAREPHYLLIN (R-3588) AND AMINOPHYLLINE

Rates*

I. M. Mercuhydrin plus intramuscular R-3588								*I. M. Mercuhydrin plus intramuscular Aminophylline*					
					Third control period								
% inc. U.V.	Na	% inc. Na	K	% inc. K	Urine	Na	K	Urine	% inc. U.V.	Na	% inc. Na	K	% inc. K
0	136.0	−6	54.9	7	3500	42.6	49.3	3970	13	119.1	180	61.0	24
196	95.0	880	40.1	49	1125	26.9	30.2	3695	228	270.0	904	45.4	50
9	180.3	224	11.2	−27	3405	74.1	14.1	5020	47	325.3	339	12.7	−10
30	75.9	319	26.8	12	—	—	—	—	—	—	—	—	—
59	121.8	357	32.5	10	2077	47.9	31.2	4228	96	238.1	474	39.7	21
I. M. Mercuhydrin plus intravenous R-3588					*Third control period*			*I. M. Mercuhydrin plus intravenous Aminophylline*					
−14	77.7	280	57.9	16	—	—	—	—	—	—	—	—	—
111	128.3	601	80.5	37	1750	38.1	67.2	2090	19	129.1	239	58.9	−12
106	237.9	325	65.5	14	—	—	—	—	—	—	—	—	—
69	18.7	316	10.5	46	560	1.2	11.5	805	44	5.1	325	9.1	−21
68	115.7	383	53.6	28	1155	19.7	39.4	1448	32	67.1	282	34.0	−17
64	118.8	370	43.1	19	2068	36.6	34.5	3116	70	169.7	397	37.4	6

% inc.—Post drug value over control value
**—Mean for Groups 2A and 2B

TABLE 3.—EFFECT OF PAREPHYLLIN (R-3588) AND NEOHYDRIN ADMINISTERED ORALLY (ALONE AND IN COMBINATION) ON WATER AND ELECTROLYTE EXCRETION AS COMPARED TO MERCUHYDRIN

	Control period			*Parephyllin alone (average 3 days)*						*Parephyllin and Neohydrin (3 days)*					
Patient	*U.V.* cc. 24 hr.	*Na excr.* mEq. 24 hr.	*K excr.* mEq. 24 hr.	*U.V.* cc. 24 hr.	% incr. U.V.	*Na excr.* mEq. 24 hr.	% incr. Na	*K excr.* mEq. 24 hr.	% incr. K	*U.V.* cc. 24 hr.	% incr. U.V.	*Na excr.* mEq. 24 hr.	% incr. Na	*K excr.* mEq. 24 hr.	% incr. K
PART A. DIURETIC RESPONSE TO PAREPHYLLIN ALONE AND IN COMBINATION WITH NEOHYDRIN (ORAL)															
L. B.	1190	53.8	25.9	798	−33	17.2	−68	16.7	−36	2642	122	202.1	276	16.6	−36
T. M.	1802	40.5	24.3	1590	−12	45.6	13	26.6	9	1863	3	108.6	168	22.9	−6
M. McW.	1180	107.7	10.8	1343	14	45.6	−58	19.4	80	1967	67	133.0	23	39.4	265
M. McE.	850	4.3	33.1	395	−54	5.9	37	19.9	−40	663	−22	34.3	698	26.4	−20
Z. D.	525	6.4	27.3	1022	95	42.6	566	35.3	29	1510	188	112.3	1655	44.8	64
V. J.	335	9.7	8.3	395	18	8.6	−11	15.5	87	478	43	15.5	60	16.3	96
A. M.	580	37.1	32.9	1245	115	8.9	−76	63.9	94	1072	85	67.5	82	43.8	33
Mean	923	37.1	23.2	970	20	24.9	58	28.2	32	1456	69	96.2	423	30.0	57
PART B. DIURETIC EFFECT OF ORAL NEOHYDRIN COMPARED TO PARENTERAL MERCUHYDRIN															
	Control period			*Neohydrin alone (average of 3 days)*						*Intramuscular Mercuhydrin*					
L. B.	1190	53.8	25.9	2315	95	145.5	170	26.8	3	1960	65	56.5	5	25.1	−3
T. M.	1802	40.5	24.3	1563	−13	127.1	214	24.8	2	—	—	—	—	—	—
M. McW.	1180	107.7	10.8	1742	48	135.6	26	47.5	340	2045	73	145.8	35	47.7	342
M. McE.	850	4.3	33.1	658	−23	19.6	356	29.4	−11	1275	50	40.2	835	39.8	20
Z. D.	525	6.4	27.3	1720	228	160.4	2406	38.8	42	1670	218	105.3	1545	34.3	26
V. J.	335	9.7	8.3	673	101	22.7	134	15.7	89	1085	224	86.3	790	28.1	239
A. M.	580	37.1	32.9	905	56	98.4	165	35.4	8	2400	314	150.2	305	87.4	166
Mean	923	37.1	23.2	1368	70	101.3	496	31.2	68	1739	157	97.4	586	43.7	132

% incr.—Percentile increase = $\frac{\text{Post Drug Observation}}{\text{Control Observation}}$

U.V.—Urine Volume
Na—Sodium
K—Potassium

vated after both the cardiac output and the renal plasma flow had returned to control levels. The prolongation of this increase was thought to be a manifestation of the direct renal effect of the drug. On the other hand, Davies and Shock[2], in studying the effect of aminophylline on renal function in congestive heart failure, found a variability in the magnitude and duration of the response to that drug. Since, in some of their cases, the xanthine produced a very transient or no increase in filtration rate, while sodium clearance was maintained at an elevated level, and since urine flow in these cases was maintained at an elevated level in spite of a transient response in filtration rate, they concluded that the diuretic effect of aminophylline is primarily the result of its action (direct or indirect) on the renal tubules. Recent work in laboratory animals is in agreement with the latter concept[9].

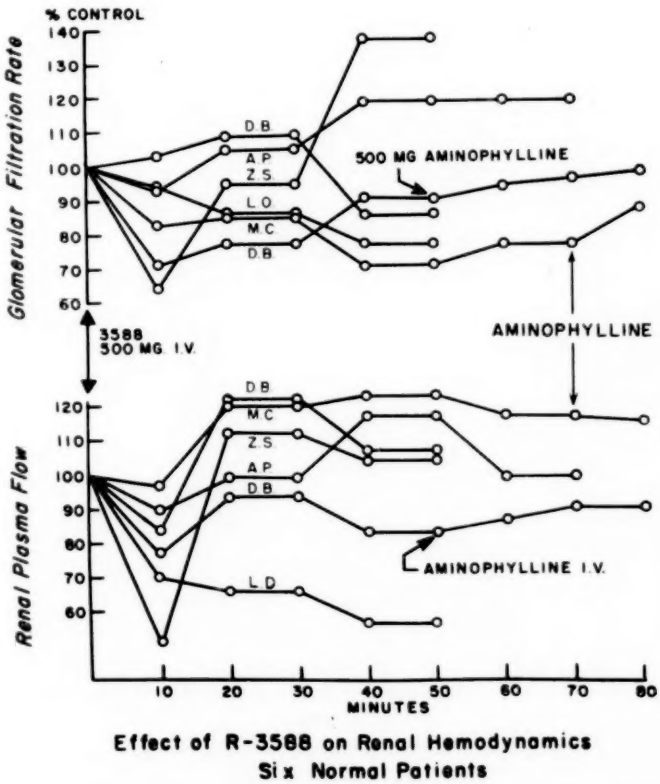

Fig. 1.—Renal hemodynamic response to intravenous Parephyllin expressed in per cent of control values in 6 normal subjects. Immediately after the drug was administered there was a sharp reduction in glomerular filtration rate and renal plasma flow. These slowly returned toward the control levels. Aminophylline administered 50 to 70 minutes later by the same route had very little effect.

Parephyllin (Riker-3588), a theophylline derivative, failed to show a significant diuretic action when given

alone intramuscularly to normal subjects (Table 1). Acute renal hemodynamic studies[8], following the intravenous administration of Parephyllin, have shown that initially both glomerular filtration rate and renal plasma flow were usually depressed in both normal subjects and patients with heart

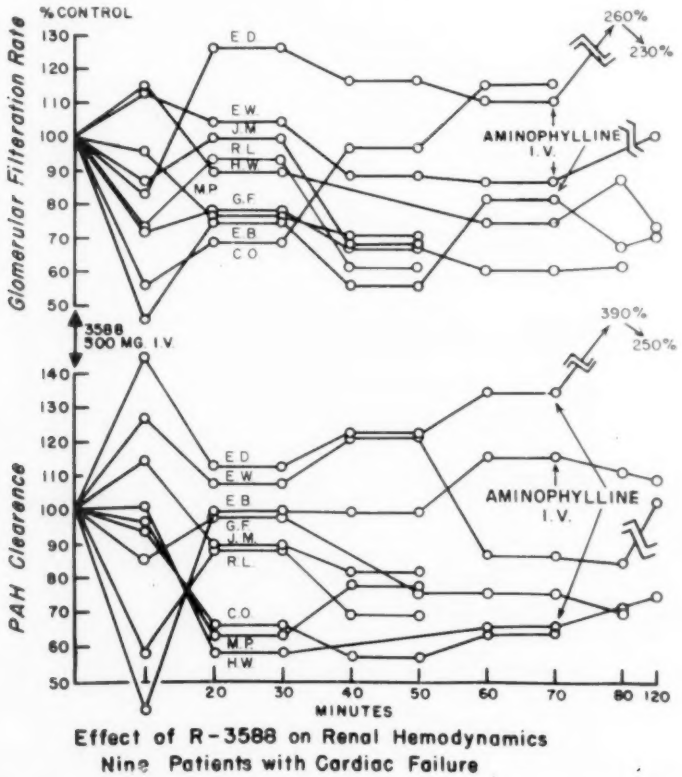

Fig. 2.—Renal hemodynamic response to Parephyllin expressed in per cent of control values in 9 patients with heart failure. There was usually a sharp reduction in glomerular filtration rate which remained depressed for longer periods than in the normal subjects (Fig. 1).

intravenously may have slightly potentiated the action of the mercurial since the total urine volume, sodium excretion and potassium excretion showed a slightly greater percentage increment over control levels than did similar values for the period of diuresis following intramuscular Mercuhydrin failure[8] (Figs. 1 and 2). This was accompanied by an acute reduction in both water and sodium excretion. The patients in cardiac failure sometimes showed an increase in sodium excretion following the initial depression[8]. When used in conjunction with Mercuhydrin in the current study, Parephyllin given alone, or following the use of intravenous aminophylline combined with intramuscular Mercuhydrin. Certainly, this response was not consistent enough to be used as a routine therapeutic procedure and offers no advantage over the xanthine derivatives already available for therapeutic pur-

poses. Used intramuscularly, neither Parephyllin nor aminophylline potentiated the diuretic action of Mercuhydrin, and the combination of Mercuhydrin and Parephyllin was less in effect than the combined use of Mercuhydrin and intramuscular aminophylline.

When given orally, Parephyllin was easily tolerated in doses of 0.6 to 1 gm. 4 times daily which, if therapeutically effective, would offer an advantage over aminophylline since the latter drug in these dosages usually causes nausea and vomiting due to gastric

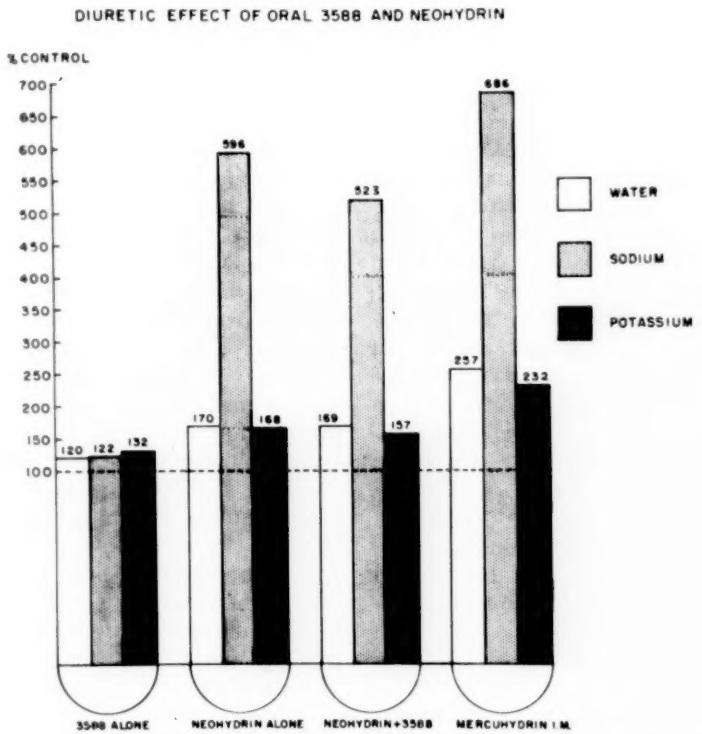

Fig. 3.—Effect of orally administered Parephyllin (R-3588) and Neohydrin on sodium, water, and potassium excretion when administered alone and in combination as compared to Mercuhydrin administered parenterally. Parephyllin has an insignificant effect on water and sodium excretion when administered alone and does not augment their excretion when administered in conjunction with Neohydrin.

Although aminophylline may be effective in augmenting mercurial diuresis in cardiac patients who are relatively resistant to mercurial diuretics, there is no evidence from the current study to suggest that it is particularly effective in this respect in patients who are responsive to mercurial diuretics.

irritation. Urine output studies showed that when used alone by the oral route, the Parephyllin had an insignificant diuretic effect (Fig. 3), as reflected in mean 24-hour urine volumes and mean 24-hour sodium excretions which were only slightly above control levels. In one patient (L.B.),

both values were decreased over control levels; in 2 patients (T.M. and M.McE.), the volume was decreased but sodium excretion was increased; while in the fourth patient (M.McH.), water excretion was augmented, while the excretion of sodium was depressed. The diuretic effect produced in the cardiac patients with the combination of oral Parephyllin and Neohydrin was thought to be due primarily to the action of the oral mercurial (Table 3). Further, the xanthine was unable to maintain the water and sodium diuresis initiated by the Neohydrin when the latter was given first in sequence.

Review of the output studies done on the patients who had received the oral medications made it possible to contrast the relative efficacy of Neohydrin, an oral mercurial, with intramuscular Mercuhydrin (Fig. 3) since each was administered in equivalent milligram doses (80 mg. per day). When Neohydrin was given alone over a 3-day period to patients in congestive heart failure, they showed a mean increment in urine volume of 70%, in sodium excretion of 496% and in potassium excretion of 68% over the control period. Mercuhydrin produced increments over control levels of 157%, 586%, and 132%, respectively. Thus, in this series, Neohydrin (administered orally) produced 44% as great an increase in 24-hour urine volume, 85% as great an increase in sodium excretion and 52% as great an increase in potassium excretion over control levels as did Mercuhydrin (administered intramuscularly) (Table 3 and Fig. 3). This compares with the report of Greiner[5] who, on the basis of dosage response studies using the patient's weight as the criterion of diuretic effect, stated that about 6 tablets (equivalent to 60 mg. Hg) of Neohydrin is equivalent in diuretic efficacy to 1.1 cc. (44 mg. Hg) of Mercuhydrin.

Conclusions. 1. Parephyllin (R-3588), a theophylline derivative, has the advantage of several possible routes of administration: intravenous, intravenously, the drug augmented intravenously, the drug augmented slightly the diuretic effect of intramuscular Mercuhydrin; however, its administration by this route was frequently associated with the appearance of dizziness, vertigo, nausea and vomiting and offered no advantage over aminophylline. Used intramuscularly, Parephyllin had only a transient diuretic effect when given alone, and when given with Mercuhydrin it did not augment the diuresis produced by the mercurial. When used orally, both aminophylline and Parephyllin did not produce a significant increase in 24-hour water and sodium excretion in patients in congestive heart failure. The diuretic effect seen in these patients when this drug was given orally in combination with Neohydrin was thought to be the effect of the oral mercurial alone.

2. Neohydrin when administered orally is an effective diuretic and when compared (on the basis of mercury content) with Mercuhydrin (administered parenterally) is about half (on the basis of increased water excretion) to three-fourths (on the basis of increased sodium excretion) as effective.

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THE EFFECT OF THE EMOTIONS ON THE PERIPHERAL CIRCULATION

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THE knowledge that emotional states affect the peripheral circulation is as old as the observation that man blushes with embarrassment, flushes with anger, or turns pale with rage or fear. Further evidence that this relationship has been recognized, if not completely understood, is provided by such familiar samples of "organ language" as "red in the face," "hot under the collar," "in the pink of condition," "cold hands, warm heart," "went into a cold sweat," "he has cold feet," "dripping with suspense." James and Lange[31] expressed it, perhaps exaggeratedly, thus: "We owe all the emotional side of our mental life, our joys and sorrows, our happy and unhappy hours, to our vasomotor system."

Although interesting, these observations were of relatively little importance medically. However, in 1862, Raynaud[59a,59b] first described a series of cases of "local asphyxia and symmetrical gangrene of the extremities." Concerning the etiology of the disease which came to bear his name, he had this to say:

"To attribute these phenomena to a fault of vasomotor innervation, was an interpretation which physiology assuredly authorized. I have further maintained that marked symmetry of the lesions ought to suggest that they originate in a discharge, either spontaneous or reflex, starting from the cord and radiating thence to the vascular nerves of the extremity . . .

"To sum up in a more definite form, I would say that in the present state of our knowledge, local asphyxia of the extremities ought to be considered as a neurosis, characterized by enormous exaggeration of the excitomotor energy of the gray parts of the spinal cord which control the vasomotor in-

nervation . . . The determining cause is often the impression of cold, sometimes even a simple mental emotion is enough."

This view seems to have been generally accepted until 1929, when Lewis[33] presented experimental evidence against it, attributing the vasospasm responsible for the clinical manifestations of the disease to a local vascular fault. Nonetheless, psychic factors were still considered at least partially responsible for attacks of the disorder and, therefore, still merited consideration in the medical approach to the problem[30]. Since Raynaud's presentation, many related reports[14,21,36,39,51,54,72,73] have been given of patients who apparently had voluntary sympathetic control, including control of the peripheral vasculature, of hysterical patients with Raynaud's syndrome, and of instances in which Raynaud's phenomena were produced by startling events.

During the past two decades, interest in the psychosomatic approach to medical problems has assumed considerable prominence. In the realm of disease attention has been directed principally toward such conditions as Raynaud's disease, in which the etiology is by no means established or simple. Perhaps more importantly, investigators in this field have been interested in learning what determines the choice of organ or organ system in the production of disease states and in prevention, if possible, of such a development. The "normal" subject has accordingly also been studied.

Physicians in ancient times believed that specific emotions caused specific changes in pulse, a belief which has persisted. Wundt[75], in the early part of this century, classified feelings in three pairs: pleasure-pain, tension-relaxation, and excitation-calm; corresponding specific changes in pulse waves for each were reported. Although this work is no longer considered valid, there are many physiologic studies of the general effects of various psychic factors on the peripheral circulation available, amply demonstrating cutaneous vasoconstriction in hands and feet during emotion.

Unpleasant emotional states are emphasized as causing the observed changes, for example, those due to vasoconstriction[4,8,10,11,22,28,29,37,48], but there is evidence that strong pleasurable emotions may give rise to identical phenomena[5]. The tendency to relax under agreeable circumstances, as shown by vasodilatation, is less easily explained. In 1906, Shepard[62] observed that directing attention to the finger in the plethysmograph was the only factor which produced vasodilatation. However, there are many recent reports[10,11,40,41,48,49] that vasodilatation does indeed take place under the proper circumstances of relaxation and comfort.

Individuals with persistent, pronounced emotional vasoconstriction display coldness of the extremities and are intolerant to cold temperatures. Such vasoconstriction may certainly aggravate the manifestations of peripheral vascular disease, particularly Raynaud's disease[2,4,15,26,32,34,38,40,42,51,52,58,61,63,70,72,73]. In addition, Osborne and Cowen[53], studying patients with trench foot, reached the conclusion that men prone to psychoneurosis, with a parallel vasomotor instability, are more susceptible to the peripheral vascular neuropathy. Rheumatoid arthritis of the hands and feet is also demonstrably influenced by the emotions, and studies have suggested that excessive vasoconstriction is associated with this disease[43,57]. Blushing and flushing have not been studied as extensively, but the old belief that easy blushing indicated a strongly paranoid personality

has not been confirmed. Vasodilatation consequent to several factors, including emotional upsets, is known to be followed by urticaria in some individuals[25].

Scattered observations indicate strongly that subjects with unstable peripheral vascular systems more readily develop conditioned reflexes involving this system than do others[24,37], suggesting a mechanism whereby the peripheral vascular system becomes the effector organ for the emotions in some individuals.

Ironically, the study of the peripheral circulation has been hampered by certain obstacles, inasmuch as its qualitative relationship with emotions is so readily discernible by even the casual observer. The major difficulty has been the lack of a technique which will yield acceptable quantitative information. Over a period of years various methods have been devised, many concerned with measurement over a given area of cutaneous temperature, the regulation of which is a function of the circulation[15,17,40,41,55,60,75,76]. Sweating and water loss from the extremities have also been used as measures for sympathetic activity and blood flow[7,35,45]. The rate of water loss from the finger tip appears to be correlated with the emotional type of the subject, being less in phlegmatic individuals than in excitable ones[45]. Several plethysmographic devices have been developed, and instruments are now available for recording sensitive, accurate and objective data[6,12,19,23,24,64,65]. With such instruments exact data concerning the emotions and their effect on the peripheral circulation in the fingers and toes should be forthcoming. It was considered worthwhile to search the literature, including almost all that written in English, for such data.

Regardless of the method employed to observe these relationships between the emotions and the peripheral vascular system, it has been necessary first to learn what the "normal" variations are for that particular laboratory procedure. Accordingly, many of the studies, particularly those in which plethysmography has been employed, have been devoted largely, or even exclusively, to this aspect of the problem[1,3,8,9,12,13,17,18,44,60,66,67]. Such factors as deep inspiration, breath-holding, smoking (tobacco or cornsilk), loud noises, sleep, ingestion of food, variations in blood pressure, spontaneous variations in vasomotor tone, varying environmental conditions, and the use, or even the sight, of various pieces of laboratory equipment have been observed to affect the blood flow. The psychic element in some of these is evident, but the vastly more important and not immediately apparent emotional factors have not been touched. There have been intriguing reports of investigation into these phenomena by various workers, but the emotional factors, although frequently mentioned, are usually given only slighting recognition[12,13,27,50,56,69,71].

Mittelmann and Wolff[49], using the Hardy radiometer to measure changes in cutaneous temperature, reported, in 1939, their observations on patients with cold hands and Raynaud's syndrome. Their purpose was ". . . (a) to study more intensively the affective states which are accompanied by skin temperature changes; (b) to determine the degree and duration of the temperature change, and (c) to ascertain the clinical significance of these reactions in subjects with cold hands and Raynaud's syndrome." Under emotional stress, a fall in cutaneous temperature occurred in 200 out of 203 observations. These emotional changes were invariably complex, although one or two emotions prevailed. In different subjects, there were found ". . . various

degrees of tension, anxiety, guilt, feelings of being pushed and of being thwarted, embarrassment, irritation, anger, rebellion, feelings of inadequacy and of being criticized or disapproved of, insecurity, humiliation, grief, feelings of helplessness, depression, despair and pleasurable excitement." The patients with Raynaud's syndrome were essentially similar to the other subjects in their reactions to induced stress, except for one striking difference: the sharp drops in cutaneous temperature were accompanied by the typical Raynaud's phenomenon, namely, pain, cyanosis, and pallor. These investigators also demonstrated that the degree of incapacity experienced by the patient was determined by the interplay of the physical factors of body warmth and the emotional state of the subject.

These same observers[41] attempted to correlate the psychologic content of the psychoanalytic interview with change in the finger temperature. Again a consistent relationship between finger temperature and various emotional reactions was demonstrable, provided the individual make-up of each subject was taken into consideration. In general, finger temperature fell when the subject encountered conditions of conflict and danger, and rose with increasing emotional security and uninhibited action.

Using cutaneous temperature as a measure of peripheral blood flow, Ostwald[55], in Germany, attempted to establish a specific relationship between relatively pure affects and the circulation of the finger tip. His observations indicated that when the subject was angry, vasoconstriction occurred, with consequent low cutaneous temperature; by contrast, elation produced the highest cutaneous temperature. When the subject was satisfied or nonparticipating, the readings fell somewhere between these two extremes, the nonparticipating individuals exhibiting the lower measurements. There is evidence, however, that such measurements are not sufficiently accurate to record quantitative fluctuations in the peripheral blood flow in response to varying emotional stimuli[16,69]. Simultaneously recorded cutaneous temperature and plethysmographic determinations do not appear to be definitely correlated.

Plethysmography has been used by many investigators to measure the changes in the peripheral blood flow, particularly in the finger and toe. The changes produced by emotions, however, have been mentioned only briefly[12,13,27,50], if at all[56,69,71]. Nevertheless, much has been learned about the circulation and the emotions with the aid of this instrument. It is worthy of note here that the alterations in blood flow in the hand do not parallel vascular responses elsewhere in the body[1,27,28,44]. Unfortunately, no plethysmograph employed to date has been entirely satisfactory. The occlusion instrument[12] has been used by many workers, but the pneumoplethysmograph described by Turner[65], in 1937, and, more recently, the portable plethysmograph of Burch and Winsor[6] seem to be more accurate and sensitive instruments.

Of the investigators of the peripheral circulation, Burch, Cohn, and Neumann[7,8,9,10,44,45,46,47,48], Burch and Ray[11], and Neumann, Lhamon and Cohn[49] have been most consistently aware of the association of emotion and changes in the peripheral blood flow and have obtained quantitative measurements of their observations by means of the plethysmograph. Burch and Ray[11] have reported a series of experiments in which plethysmograms were recorded on medical students. The subjects were permitted to rest in bed in a comfortable air-conditioned

room, especially designed to minimize external psychic influences. During recording of the plethysmograms, psychic disturbances were produced by various methods, including entrance of the observer (who also happened to be an instructor of the students), frowning at the subject and questioning him, dropping a book in an adjacent room, pressing a buzzer, talking loud, and presenting problems of mental arithmetic. All of these evoked demonstrable reactions, characterized by reduction in volume of the pulsatile deflections and in total volume of the part. In addition, there were changes in the alpha deflections, which became small and more irregular, and occurred at a more rapid rate than in the normal, relaxed subject.

The appearance of the plethysmographic tracings suggested a classification[8]. Of the five major waves, that is, pulse, respiratory, alpha, beta, and gamma, the alpha deflections were distinguishable as of three specific types: Type I, all deflections small; Type II, deflections intermediate in size; Type III, wide range in size of deflections. It was also possible to make certain generalization about the personalities of the subjects in whom these waves were found. Thus, the subjects with Type I alpha waves were placid and emotionally stable individuals who could be depended upon to make little of disturbing conditions in their environment and who adjusted easily to the physiologic procedure. Type III waves were observed in subjects who were inquisitive and, at times, anxious about the experimental procedure. These people frequently had to be asked to remain quiet during the period of observation. Although it was impossible to know what these subjects were thinking, it was observed that their occasional spontaneous remarks were followed shortly by pronounced vasoconstriction, particularly if an unpleasant thought or subject arose.

With this background, Neumann, Lhamon, and Cohn[49] investigated further the relationship between plethysmographic variations and the emotional state of the subject. Under constant environmental conditions, they attempted to obtain parallel records of the pattern of changes in finger volume and a description of the subject's affect. The emotional states studied and defined by the authors were contentment, elation, sadness, anxiety, depression, and resentment. The customary type I, II, and III records of alpha deflections were obtained. It was noted that the pulse waves, too, varied in a characteristic fashion, independently of the alpha waves. Some records showed all large pulse waves, called "A"; some revealed all small waves, called "B"; and others, both large and small waves at different times, labeled "C". Theoretically, nine combinations were possible, but only eight were actually found: IA, IB, IC, IIA, IIB, IIC, IIIA, and IIIC. Intense anxiety was accompanied by a Type IB record. Contentment was usually associated with IA, a type of record obtained only when the patient was completely relaxed. There were two variants with this state, IIA and IC. Anxiety of moderate degree, elation, and resentment were all reported in those instances in which a IIIC recording was obtained. With slight resentment, slight anxiety, sadness, or a combination of emotions in which no affect was dominant, the intermediate types IIA, IIB, IIC, and IIIA were obtained. No uniformity of tracing was noted when depression was reported, one tracing each of IIC, IIIC, and IA being noted. These observations suggest that persons of different psychologic types are likely to exhibit characteristic pulse and alpha waves.

Van der Merwe[68] studied two groups of psychoneurotic subjects, using the optical finger plethysmograph to measure change in finger volume and the Bell Adjustment Inventory (Student Form) to measure emotional adjustment. One group displayed symptoms of anxiety and the other manifestations of an hysterical and neurasthenic nature. Both groups of subjects exhibited disturbed basic emotional tension, and there seemed to be a significant relationship between the emotionality of the subjects and their scores of peripheral vasomotor function. Those with anxiety demonstrated vasoconstriction, whereas those with hysteria and neurasthenia appeared less tense and showed more dilatation. Theron[64], using the same plethysmographic method to study a group of 50 normal individuals, reported that labile persons, subjected to a simple mental test, tend to have a greater rate of change in finger volume than do stable ones.

During the course of plethysmographic studies on many subjects, some interesting observations on hypertension, which seem worthy of reporting briefly, have been made. In 1942, Neumann, Cohn, and Burch[18], who were interested in the effect of the subject's surroundings upon his peripheral vascular reactions during the experiment, reported results of two series of experiments performed with normal individuals, hypertensive patients, and senile individuals as subjects. In the first series, plethysmograms were made in a laboratory setting. Most subjects, and particularly the hypertensive ones, became tense and apprehensive under these conditions. The recordings indicated that initial relaxation was extremely difficult to obtain in the hypertensive and senile groups. These same authors[10] observed that the hypertensive patients were conspicuous in their inability to relax and in their tendency to be psychologically disturbed. Different stimuli varied in their ability to produce extreme apprehension in particular individuals, but of particular interest was the observation that stimuli which would ordinarily be considered innocuous were capable of interfering with relaxation. The hypertensive subjects, all of whom were emotionally unstable or excitable, in no case had Type I alpha wave records[47] but rather either Type II or Type III. The alpha waves for senile subjects in the same series of experiments were all of Type I.

Summary and Conclusions. The use of plethysmography in studying normal subjects as well as patients with various types of cardiovascular disease has amply confirmed the old observation that peripheral blood vessels are easily influenced by psychic factors. The chief obstacle to extensive study in the past has been lack of a satisfactory instrument for objective quantitative measurement of changes in the peripheral circulation of the extremities. With the recent development of a practical type of plethysmograph, which is also accurate and sensitive, considerable data relative to this subject should be forthcoming. Here is perhaps a unique opportunity to observe end organs which are readily accessible and are extremely sensitive to mental processes at both conscious and unconscious levels, with the aid of an instrument capable of recording small and sudden changes in the peripheral vasculature.

A survey of the literature indicates that only the surface of the problem has been skimmed. It should be stressed, therefore, that a knowledge of the variations which occur in the blood vessels of the digits may assist in better understanding of other portions of the

cardiovascular system, a field in which every fragment of information can be helpful. And to the psychiatrist or psychosomatically oriented individual in any other field of medicine, the discovery of a tool which, by objective measurements, may yield quantitative and specific information about emotional and mental processes should be welcomed as a valuable aid in clarifying some of the basic problems in this field.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF OCTOBER 20, 1953

Electrolyte Composition of Tubule Preliminary Study.* PHYLLIS A. BOTT, PH.D. (Dept. of Physiol. Chem., Woman's Med. Coll. of Penna.) Samples of tubule fluid collected from the kidneys of Necturi by the Methods of Wearn and Richards (Am. J. Physiol., **71,** 209, 1924) and Richards and Walker (Am. J. Physiol., **118,** 111, 1937) were analyzed for potassium (Fed. Proc. **10,** 165, 1951) and inulin (Am. J. Physiol., **168,** 107, 1952) and the results compared with those on serum in the same animals. Although there is some variability the concentration of potassium decreases progressively along the proximal tubule, finally reaching a value at the end of this segment only 20% of that in serum. The potassium concentration ratio/inulin concentration ratio also falls over this region. In the distal tubule the potassium appears to rise in general, and in some cases reaches values higher than those of serum. Although potassium/inulin ratios also appear to rise, they have never reached 1.0. Since each result obtained is from a different animal, potassium secretion has not been proved although possibly it is suggested. A few experiments were performed in which sodium, (J. Biol. Chem., **147,** 653, 1943) potassium and chloride (Westfall, Findley and Richards, J. Biol. Chem., **107,** 661, 1934) as well as inulin were determined. Although preliminary, they suggest that the concentration of sodium remains approximately the same as that in serum at least over the first half of the proximal tubule, while chloride rises slightly over this region. Chloride results are therefore much like those of Walker, Hudson, Findley and Richards (Am. J. Physiol., **118,** 121, 1937). Inulin increases here more than chloride. Both sodium and chloride fall off to very low values in the distal tubule as inulin concentration rises.

Studies on the Biosynthesis of Pyrimidines. C. COOPER, PH.D., AND D. W. WILSON, PH.D. (Dept. of Physiological Chemistry, Univ. of Penna.). Pyrimidines occur in nucleic acids which are important in the metabolism of all cells. Orotic acid (OA) is known to be converted into the pyrimidines of nucleic acid.

Homogenates of rat liver were found capable of converting ureidosuccinic acid (US) to OA by way of dihydroorotic acid (DHO). Homogenates of rat liver were incubated with either C^{14}-US or C^{14}-DHO and the amount converted to OA determined. While the latter attained a maximal conversion in 30 minutes, the former required 180 minutes. The conversion of US to DHO was demonstrated.

Because of the close structural similarity of US to an intermediate of the urea cycle, arginosuccinic acid, it was thought that perhaps the urea cycle was involved in the biosynthesis of pyrimidines. *L*-citrulline labeled with

*This work was supported in part by a grant from the Life Insurance Medical Research Fund.

C^{14} and N^{15} in the carbamyl moiety was administered to rats *in vivo*. Analysis of the isotopic content of the nucleic acid purines and pyrimidines, the respiratory CO_2, the urinary ammonia, and the urinary urea demonstrated that the urea cycle and citrulline are not involved in pyrimidine formation.

Slices of regenerating rat liver were incubated with either OA, US, or AF. With OA as precursor, the isotope was incorporated twice as well into the uracil as into the cytosine. If the other compounds were utilized by way of OA, one might expect that the isotope dilution would be greater but that the relative incorporation into the uracil and cytosine would be the same. This fact is expressed by dilution ratios which were identical when OA and US were compared. This indicates that US is utilized by way of OA. When OA and AF were compared, however, entirely different results were obtained. This indicates that two different pathways exist in mammals for the biosynthesis of pyrimidines, one of which involves OA and the other does not.

Before these experiments could be conducted, a method for the preparation of DHO had to be perfected, since the method of synthesis described in the literature does not yield DHO. The preparation was achieved by the hydrogenation of orotic acid, employing an unusually high catalyst-to-substrate ratio and a prolonged period of hydrogenation.

The Role of Thoracic Tension Receptors in the Reflex Peripheral Vasodilatation Induced by Intravenous Epinephrine. CARL C. GRUHZIT, M.D., PH.D., and GORDON K. MOE, PH.D., M.D. (Dept. of Physiology, State University of New York, Upstate Medical Center, Syracuse). The intravenous injection of 0.2 to 2.0 microgm./kg. of epinephrine in dogs results in a marked increase in femoral blood flow. This response occurs in the innervated separately perfused leg when epinephrine is administered to the trunk of the animal, and is therefore not dependent on the local action of epinephrine but must involve neurogenic factors. The peripheral vasodilatation is also not dependent on the integrity of the carotid sinus and aortic arch pressoceptors, since it occurs when alterations in systemic pressure are prevented by means of a pressure regulator, or when the vagi and carotid sinus nerves have been sectioned. This reflex is, however, related to the cardiac action of epinephrine, since reflex femoral vasodilatation may be elicited by injections of epinephrine into the left auricle or ventricle but not by systemic arterial injections. The response is not significantly altered by cardiac or pulmonary denervation or by thoracic sympathectomy but is abolished by thoracic dorsal root section. Procedures such as rhythmical tugging on the thoracic aorta or increasing thoracic aortic pulse pressure which, to some extent, mimic the effect of increased cardiac activity on the thoracic aorta produce femoral vasodilatation. In addition, this reflex may be blocked by the application of local anesthetics to the region of the thoracic aorta or by clamping and restraining the thoracic aorta during the administration of epinephrine. It appears likely, therefore, that the reflex peripheral vasodilatation induced by epinephrine depends to a large extent on the stimulation by increased cardiac activity of tension receptors which are located in the region of the thoracic aorta and whose afferents run via the thoracic dorsal roots. This reflex may play the major role in regulating the redistribution of blood following the administration of epinephrine.

Effect of the Addition of CO_2 to a High Oxygen Gas Mixture on the Skin Oxygen Tension. SEARLE K. WELLING, B.A., and RAYMOND PENNEYS, M.D. (Vascular Sect., Robinette Fdtn., Hosp. Univ. Penna.) The comparative effects of inhalation of pure O_2 and 95% O_2-5% CO_2 on the oxygen tension of the warm, vasodilated skin were studied to determine if the addition of CO_2 to a gas of high O_2 concentration would further increase the skin oxygen tension above that obtained with pure O_2. Skin oxygen tension was measured by the polarographic method using the platinum tipped electrode. The tension values obtained with inhalation of pure O_2 and those with 95% O_2-5% CO_2 were measured in 12 experiments on 8, healthy adults using 4 electrodes in each experiment. Each subject first breathed pure O_2 for a period sufficiently long to produce stability of the skin tension. Then the CO_2 mixture was inhaled for a similar period, followed finally by a second period on pure O_2. The two stable readings on pure O_2 were averaged and compared to the stable reading obtained with the CO_2 mixture. A rapid skin blood flow, as measured by the skin temperature, was maintained throughout the experiment.

In these 12 experiments, the 95% O_2-5% CO_2 gas mixture gave a consistently higher skin oxygen tension than that obtained with the pure O_2. The additional increase resulting from the CO_2 mixture averaged 13% (0 to 29%).

This increase in the skin oxygen tension is interpreted as reflecting a similar change in the arterial oxygen tension.

BOOK REVIEWS AND NOTICES

PEPTIC ULCER: PAIN PATTERNS, DIAGNOSIS AND TREATMENT. By LUCIAN A. SMITH, M.D., Asst. Prof. of Medicine, Mayo Foundation, and ANDREW B. RIVERS, M.D., Late Assoc. Prof. of Medicine, Mayo Foundation. Pp. 595; 208 ills. New York: Appleton-Century-Crofts, Inc., 1953. Price, $12.50.

As its title indicates, this book is primarily concerned with the varying symptomatic expressions of peptic ulcer disease, the mechanisms responsible for these expressions, and their medical treatment. Although it comes not long after the appearance of other more extensive and comprehensive volumes dealing with peptic ulcer, the book is distinctive because of the emphasis placed on the symptom of pain and its significance. The late Dr. Rivers throughout his life was a devoted student of ulcer pain and Dr. Smith has continued this interest. The book carries the authority of their careful observations complemented by the vast experience of the Mayo Clinic. The text is attractively printed and arranged, is written in a style which makes for easy reading, and is well supported by illustrative case histories. In addition, an appendix of diets is included along with suggestions for patient education. Much of practical value is to be found in this book, even for those well acquainted with peptic ulcer disease and its manifestations. J. B.

LECTURES ON THE SCIENTIFIC BASIS OF MEDICINE. VOLUME I, 1951-52. British Postgraduate Medical Federation, University of London. Pp. 396. 91 ills. London: The Athlone Press, 1953 (U. S. Agents: John de Graff, New York). Price, $6.00.

INCLUDED in this first annual volume are 18 of the 39 lectures delivered at the meetings of the British Postgraduate Medical Federation during the winter of 1951-52. The lectures have been "intended for younger research workers and teachers in the pre-clinical and clinical sciences and for junior clinicians who hope to find careers as consultants and teachers in the various special branches of medicine and surgery." A wide range of subjects has been covered, subjects in which very significant advances are being made at the present time. The initial lecture by E. D. Adrian on "The Scientific Approach to Medical Research" is one that should be read by all would-be investigators. Following it there are discussions of adrenal hormones, mammary function, cortical mechanisms, hemorrhage and the cardiovascular system, the lability of blood pressure, visual sensation, tissue response to injury, renal physiology and pathophysiology, antibacterial immunity, viruses, blood coagulation, ageing, adolescent growth, nutritional assessment, and the biological action of radiation. The lecturers have been selected because of their contributions to their respective fields, and they constitute an impressive array indeed. This volume is highly recommended to those for whom it was intended, and it is to be hoped that subsequent volumes of similar merit will be forthcoming through the succeeding years.

T. D.

TUMORS OF THE ORBIT. By RAYMOND G. INGALLS, M.D., Formerly Instructor and Assistant Eye Pathologist, College of Physicians and Surgeons, Columbia University. Pp. 410; 140 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $11.50.

THIS text is based on the analysis of a large group of adequately studied case histories, collected from the works of a group of physicians.

It is pleasing, brief and factual. It serves as an excellent reference for those whose experience is not extensive in orbital tumors.

G. G.

THE UNIPOLAR ELECTROCARDIOGRAM. A CLINICAL INTERPRETATION. By JOSEPH M. BARKER, M.D. Pp. 655; 458 ills. New York: Appleton-Century-Crofts, Inc., 1952. Price, $12.50.

THE late, great Frank N. Wilson, who contributed so extensively to our present-day knowledge of basic electrocardiography, made it very evident in his writings that successful interpretation of tracings must be dependent, not upon memorizing characteristic patterns, but upon acquaintance with the electrical and physiologic principles by which these patterns are determined. It had been the hope of a host of Dr. Wilson's admirers that he would bring together in one volume a summary of his extensive knowledge of the subject, but the Master was too busily engaged in extending the frontiers of knowledge to take time for a work of this sort. Fortunately,

one of Dr. Wilson's students, who is extremely well equipped for the job, has prepared for the practitioner a volume presenting the important theoretical and practical phases of unipolar electrocardiography. The reviewer knows of no better way for the one who would learn the Wilsonian concepts and who would thus prepare himself to be a first class electrocardiographer than to read and re-read and make part of himself the contents of this volume. The author has done a splendid job of clarifying a difficult subject by lucid writing, excellent diagrammatic figures and well chosen electrocardiograms. It is to be hoped that this book will do much to do away with the all too frequent slipshod reading of electrocardiograms which is so prevalent today. T. D.

PIGMENT CELL GROWTH. PROCEEDINGS OF THE THIRD CONFERENCE ON THE BIOLOGY OF NORMAL AND ATYPICAL PIGMENT CELL GROWTH. Edited by MYRON GORDON, New York Zoological Society. Pp. 365. New York: Academic Press, Inc., 1953. Price, $7.00.

THIS book is a collection of 22 papers by 38 authors read at the Third Conference on the Biology of Normal and Atypical Pigment Cell Growth held in New York in 1951. Only 3 of the 22 papers deal directly with the practical aspects of the diagnosis and therapy of the malignant melanoma in man. It will be of most interest, therefore, not to the practicing clinician but to the research worker in the field and possibly to dermatologists and oncologists who wish to broaden their knowledge on the subject. E. A.

THE HUMAN PELVIS. By CARL C. FRANCIS, M.D., Asst. Prof. of Anatomy, Western Reserve University. Pp. 210; 59 ills., one in color. St. Louis: C. V. Mosby Co., 1952. Price, $5.00.

THIS small book presents in a concise form much of the information which the surgeon needs to know concerning the anatomy of the pelvis. In connection with the subjects discussed in the book the author has reviewed what he considers to be significant articles that are backed by careful observation of an adequate amount of material. He has handled the confusion which exists in terminology by giving many synonyms where it is necessary. The illustrations, all but one of which are black and white, supplement the text in a satisfactory fashion. If one were to become familiar with the material contained in this book, he would have an adequate working knowledge of the pelvic area. J. H.

THE INCIDENCE OF PEPTIC ULCER IN DENMARK. By GUNNAR ALSTED, M.D., Privat-Docent of the University of Copenhagen, Director of Health Bureau, League of Red Cross Societies, Geneva. Pp. 88; 13 ills. Copenhagen: Danish Science Press, Ltd., 1953. Price, $2.25.

THE reviewer would commend this study to the attention of anyone interested in the problem of peptic ulcer. It presents a statistical study on the clinical incidence of gastric and duodenal ulcer in Denmark, a country especially suited for such a survey, not only because of its comparatively small and racially uniform population, but because of its excellent public health service. As a result, the author could evaluate various factors more directly concerned with the incidence of this disease freed of some very important and usually confusing variables when such a study is attempted in an area of a mixed population. H. S.

MICROBIOLOGY AND PATHOLOGY. By CHARLES F. CARTER, M.D., St. Louis Southwestern Railway Hospital, Texarkana, Arkansas, and ALICE L. SMITH, M.D., Parkland Hospital School of Nursing, Dallas, Texas. 5th ed. Pp. 847; 260 ills. St. Louis: C. V. Mosby Co., 1953. Price, $5.50.

THE first 463 pages of this volume are devoted to microbiology, the remaining 320 to pathology. Both sections are somewhat catalogue in extent and manner of presentation. The two parts are presented in such fashion as to have little relation to each other and this reviewer fails to see the advantage in combining them under one cover unless it be for the purpose of transportation. The volume is apparently intended for the training of nurses. E. A.

DISEASES OF THE DIGESTIVE SYSTEM. By SIDNEY A. PORTIS, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Illinois Medical School. 3rd ed. Pp. 1119; 274 ills. Philadelphia: Lea & Febiger, 1953. Price, $20.00.

THIS book has 57 contributors, each writing upon topics of their special interest. As

is true in such texts, there is an unevenness of presentation both in regard to content and literary style. The second edition of this book published in 1944 has been revised, including the addition of several chapters on psychodynamics and psychogenesis of gastrointestinal dysfunction. A one-volume text on gastroenterology must necessarily treat many subjects briefly, but the reviewer feels that the chapters on diseases of the liver and pancreas might have been extended. The management of hemorrhage from esophageal varices and postgastrectomy syndrome is not discussed. The book will prove of value to medical students and internists as a source of references. Lists of selected references are appended to the various chapters.

D. S.

CHRONIC PULMONARY EMPHYSEMA. By MAURICE S. SEGAL, M.D., and M. J. DULFANO, M.D. New York: Grune & Stratton, 1953. Price, $5.50.

THIS book is an enlargement of lectures on the management of chronic pulmonary emphysema given by the senior author over a period of years. It is an unusually successful attempt to integrate physiologic aspects with treatment of this common disabling and distressing pulmonary disease. In direct and lucid style the authors discuss the development of chronic pulmonary emphysema, its clinical features and management, placing emphasis on the derangement of breathing function that accounts for symptoms and that determines logical therapy. Special attention is given to the various complications of the disease itself and of "paradoxic therapeutics." The detailed accounts of the use of ACTH and cortisone, oxygen, pneumoperitoneum and aerosols are practical and up-to-date. The book includes an extensive bibliography and a useful appendix on methods of performing pulmonary function tests. D. O.

IMMUNITY, HYPERSENSITIVITY AND SEROLOGY. By SIDNEY RAFFEL, M.D., Stanford University School of Medicine. Pp. 531; 58 ills. New York: Appleton-Century-Crofts, Inc., 1953. Price, $8.00.

DR. RAFFEL has produced *the* modern textbook of immunology. It is modern in the sense that it covers the literature through 1951. But this fact in itself is relatively unimportant. The real value lies in the manner with which the author explains immunologic phenomena in light of recent advances in immunochemistry, endocrinology and radiobiology. Because host-parasite relationships are exceedingly complex, the high degree of clarity achieved by Dr. Raffel reflects an orderly mind, a real command of the subject and a great deal of work.

Certain features of this text deserve comment. The author has made a significant contribution to the teaching literature by insisting that the processes of immunity, hypersensitivity and serology be considered as separate and distinct entities. Also commendable is his practice of subjecting research findings to critical evaluation. But in doing so the author's own views are quite evident as, for example, in the relationship of the hypersensitive state to immunity where the arguments in favor of Arnold Rich's views predominate. Section Three is somewhat unsatisfactory in that it is neither here nor there. Among twelve infections selected for detailed discussion, the author included botulism for which there is nothing of interest; whereas he omitted streptococcal infections with their highly important immunologic patterns.

This is not a textbook for the sophomore medical students who generally are denied the time they would need to digest it. Rather, it is a most important tool for their teachers and for students taking separate courses in immunology. And for all investigators and clinicians concerned with the broad aspects of immunology, it is highly recommended.

E. S.

AN ATLAS OF SURGICAL EXPOSURES OF THE EXTREMITIES. By SAM W. BANKS, M.D., and HAROLD LAUFMAN, M.D., Ph.D., Northwestern University Medical School. Pp. 379; 550 ills., 179 plates. Philadelphia: W. B. Saunders Co., 1953. Price, $15.00.

THIS book is an outstanding one in its field and is certain to take a place among the classics of surgical atlases of the present day. It covers the entire field of surgical exposure of the extremities. The illustrations are of excellent caliber and the lettering is clear and adequate. In conjunction with each plate, on which by drawing the method of surgical exposure of the particular portion of the extremity is illustrated, there is a brief description of the procedure which complements the drawing.

This book would be of real value in the library of all orthopedists and any general surgeon who is concerned with surgical treatment of the extremities. It should be in the surgical libraries of hospitals and also be available for residents and internes. H. C.

VISUAL ANATOMY: THORAX AND ABDOMEN. By SYDNEY M. FRIEDMAN, M.D., Ph.D., Professor of Anatomy, University of British Columbia. Pp. 203; 107 ills., 20 in color. Springfield, Ill.: Charles C Thomas, 1952. Price, $10.50.

THIS is the second volume of Visual Anatomy, the first one having dealt with the Head and Neck. The book is designed as a review for the student who has already completed a dissection of the body. Alternate pages present pictures with the opposing page carrying supplementary written description. The approach is a logical one in which the skeletal framework is first described and then related structures are placed upon it in order as one progresses from the posterior aspect anteriorly. This mode of organization of the material gives an excellent concept of the relationship of the structures to each other and to the skeletal framework. This book should very adequately serve the purpose for which it is intended, both for the undergraduate and the postgraduate student.

J. H.

PHYSICAL EXAMINATION OF THE SURGICAL PATIENT. By J. ENGLEBERT DUNPHY, M.D., Professor of Surgery, Harvard Medical School and THOMAS W. BOTSFORD, M.D., Clinical Associate in Surgery, Harvard Medical School. Pp. 326; 188 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $7.50.

THIS excellent, concise text fills an existing gap between the standard texts of physical diagnosis and the surgical textbook. Most books on physical diagnosis are written by internists and lack many of the finer points of surgical diagnosis which these authors have presented.

The drawings are clear and the discussion is well arranged.

This book is recommended as a supplement to the standard course in physical diagnosis for medical students and is highly recommended for all those who are desirous of increasing their diagnostic acumen in surgical diseases.

R. B.

RELAX AND LIVE. By JOSEPH A. KENNEDY, Assistant Physical-Training Director of the Y.M.C.A., Atlanta, Georgia. Pp. 205. New York: Prentice-Hall, 1953. Price, $3.95.

THE author presents his methods for achieving relaxation of muscles, respiration and mind. Separating his subject into "passive" relaxation for rest and recuperation, and "rhythmic" relaxation for endurance without fatigue when things must be done, the author has specific ideas for each.

Loosely based upon physiological theories, the success depends upon mastering a routine of voluntary maneuvers which is said to result in relaxation. This must be achieved at the expense of displacing the tensions, but what happens is not entirely clear.

The nonspecific exercise therapy described here may help some relax.

H. F.

PHEOCHROMOCYTOMA AND THE GENERAL PRACTITIONER. By JOSEPH L. DECOURCY, M.D., and CORNELIUS B. DECOURCY, M.D., DeCourcy Clinic, Cincinnati, Ohio. Pp. 165. Cincinnati: DeCourcy Clinic, 1952. Price not given.

THIS small volume has been prepared to thoroughly acquaint the general practitioner with the "great mimic" amongst hypertensive disorders, the pheochromocytoma. After introductory sections which include an historical résumé and a group of illustrative case histories, the pathology, pathophysiology and clinical picture are summarized, and the differential diagnosis presented. The sections dealing with the various diagnostic tests available to the physician are very well done. The final chapter covers the various surgical considerations which are of importance in removing the tumor. The bibliography includes 361 references. Every physician who is not thoroughly acquainted with the diagnostic features of the pheochromocytoma should carefully read this book.

T. D.

MORRIS' HUMAN ANATOMY. Edited by J. PARSONS SCHAEFFER, M.D., Prof. of Anatomy Emeritus, Jefferson Medical College. 11th ed. Pp. 1718; 1220 ills. New York: Blakiston Co., 1953. Price, $16.00.

NOTATION that the eleventh edition of this highly respected and widely used textbook exceeds the previous edition by nearly 100 pages would in no way give a correct idea of the painstaking effort which has obviously gone into its production. Many sections have been extensively rewritten and numerous new illustrations are included. Contributors new to this edition are Professors E. Lachman, J. E. Markee, C. G. Smith and M. Trotter.

Throughout the volume rearrangement of the valuable finer print paragraphs (concerning actions, relations, variations, embryology,

clinical aspects, and others) into double column format should undoubtedly prove helpful to the reader whether he be medical student or clinician. Highly commendable also is the change made in this edition from consecutive listing to a modern, clear and attractive manner of presentation of the reference citations at the close of each section. Uniformly well edited, Morris' is probably the most comprehensive and accurate textbook of human anatomy available today. N. B.

THE SCIENTISTS LOOK AT OUR WORLD. By WILLIAM V. HOUSTON, W. ALBERT NOYES, JR., CURT STERN, ALAN GREGG AND WENDELL H. CAMP. Edited by JOHN M. FOGG, JR. Pp. 147. Philadelphia: University of Pennsylvania Press, 1952. Price, $3.00.

THIS is a collection of the five Benjamin Franklin Lectures given at the University of Pennsylvania in 1951 by William V. Houston, President of Rice Institute; Walbert A. Noyes, Jr., Chief of the Chemistry Department of the University of Rochester; Curt Stern, Editor of Genetics; Alan Gregg, Director of Medical Science in the Rockefeller Foundation; and Wendell H. Camp, Curator of the Department of Experimental Botany and Horticulture of the Academy of Natural Sciences in Philadelphia. A physicist, a chemist, a geneticist, a physician, and a botanist, each a recognized leader in his field, discuss the major advances that have occurred in those fields in recent years. Each also stresses the interdependence of the many fields of science and the responsibility of the scientist to society. Here is a compact postgraduate course in five major and modern sciences that every physician can profit by. R. K.

DOCTORS BY THEMSELVES. By EDWARD F. GRIFFITH, M.R.C.S., L.R.C.P. Pp. 614; 64 ills. London: Cassell & Co., Ltd., 1952 (The British Book Centre, Inc., New York, U. S. Agents). Price, $4.50.

THIS is a remarkable collection of 869 citations, a few lines to several pages each, from the writings of nearly 400 physicians, both ancient and modern, and a few others, that gives a composite picture of the many-sided men that physicians so often are. The quotations are arranged in groups: The Doctor at Work; The Doctor Amuses Himself; The Doctor's Troubles (these are notably military); The Doctor Looks at Life; Life, Death and Immortality. A section at the end gives brief biographical sketches of those whose writings were drawn upon. The book makes excellent bedtime reading. It is warmly recommended. R. K.

PHARMACOLOGY IN CLINICAL PRACTICE. By HARRY BECKMAN, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry. Pp. 839; 152 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $12.50.

THE author has divided the subject matter into two parts. The first section deals with the pharmacological action of the drugs. The second section deals with the chemical and physical properties, the clinical indications and the dosage of the drugs. The book is well written and is highly recommended as a reference book for the general practitioner. C. B.

WORLD HEALTH ORGANIZATION TECHNICAL REPORT SERIES NOS. 46 AND 54. EXPERT COMMITTEE ON INSECTICIDES. THIRD AND FOURTH REPORTS. Pp. 36 and 98; 1 and 11 ills. Geneva: World Health Organization, 1952. Prices, $.25 and $.65 respectively.

VALUABLE information on specifications for insecticides, and for the manifold apparatus used in their preparation, preservation and application, with appropriate test procedures for checking materials. R. K.

MILITARY MEDICAL MANUAL. 7th ed. Pp. 761; illustrated. Harrisburg: The Military Service Publishing Co., 1952. Price, not given.

THIS unofficial publication, now in its 7th edition, has made itself not only increasingly useful but almost indispensable for both officers and enlisted men of the Armed Medical Services. As Surgeon General Armstrong points out in his Foreword, the book is particularly useful because within the covers of a single volume is found excellent coverage of most subjects needed by commanding officers of field medical units. Part 1 deals with purely military matters of which medical officers need to have a working knowledge. Part 2 is devoted to professional subjects that are the responsibility of medical personnel. Part 3 gives complete and detailed information on the technical employment of medical units in support of combat operations. The new edition has been brought thoroughly

up-to-date with additional material based on more recent experience including the medical aspects of atomic, biological and chemical warfare. R. K.

ANNUAL REVIEW OF BIOCHEMISTRY, Vol. 21, 1952. Edited by J. MURRAY LUCK, HUBERT S. LORING, and GORDON MACKINNEY. Pp. 781. Stanford, California: Annual Reviews, Inc., 1952. Price, $6.00.

WITH this volume, as the editors note, the Annual Review of Biochemistry comes of age. The general high level of excellence of this series has been maintained by the 34 workers who contribute 23 sections to the present review. Included are comprehensive appraisals of the year's research on the chemistry of carbohydrates and carbohydrate metabolism, on the chemistry of amino acids and proteins and their metabolism and on the chemistry of lipids and fat metabolism. Other sections deal with comparative biochemistry, nutrition, the biochemistry of muscle, of neoplastic tissue, of antibiotics, and of various hormones, vitamins, and enzymes.

Although the entire volume may be read with profit, the review chapter dealing with water soluble vitamins which are concerned with one- and two-carbon intermediates is particularly valuable and stimulating.

C. Z.

REVISTA DE INVESTIGACION CLINICA. ORGANO DEL HOSPITAL DE ENFERMEDADES DE LA NUTRICION, MEXICO, Volume XV, April and July, 1952, Nos. 2 and 3. Pp. 164; illustrated. Price not given.

THE medical profession of Mexico and the School of Medicine in Mexico City have suffered a great loss in the untimely death, at the age of 41, of Dr. Esteban Maqueo Tapete, Professor of Medicine. The Hospital of the Diseases of Nutrition dedicates this special number of its excellent journal, Revista de Investigación Clínica, with 10 articles by 21 of his colleagues, covering a variety of clinical subjects, to his memory. R. K.

WEGE VERGLEICHENDER THERAPIE IN DER INNEREN MEDIZIN. III. RUHR. IV. KRIEGSNEPHRITIDEN. V. MENINGOKOKKENINFECTIONEN. BY ROBERT E. MARK, M.D. Pp. 296; 76 ills. Munich: Urban & Schwarzenberg, 1952. Price, DM 30.

THIS number includes three chapters (pages 419 to 715) of the book "Wege vergleichender Therapie in der inneren Medizin." The first deals with the enteritides in a contained population (the observations were made in three camps of military prisoners in Germany during World War II) particularly with regard to evaluation of methods of treatment. Polyvalent Shigella serum was less useful than sulfonamide therapy. The second chapter deals with "war nephritides" and gives some practical observations on the management of over 1400 personally observed cases. In the third chapter are discussed comparative values of immune serum and sulfonamides in the treatment of meningococcal infections, with a decision in favor of the latter. There are numerous useful clinical and epidemiological observations and surveys of pertinent literature. Those interested in these fields who can read German will find this a valuable publication. R. K.

PROGRESS IN FUNDAMENTAL MEDICINE. Edited by J. F. A. MCMANUS. Pp. 316; 74 ills. including 2 color plates. Philadelphia: Lea & Febiger, 1952. Price, $9.00.

THIS splendid volume consists of a series of authoritative discussions on certain subjects of broad medical importance. The range of topics is wide, as can be noted from the chapter headings: Parenteral Nutrition with Particular Reference to Protein Hydrolysates, Melanotic Tumors of the Skin, Pathology of Systemic Lupus Erythematosus, Diagnosis of Fungus Infections with Particular Reference to Staining Methods, The Liver, Techniques for the Histochemical Approach to Pathology, Coronary Artery Disease, Carcinoma in Situ of the Cervix Uteri, and Non-Silica Pneumoconioses.

Workers in both the clinical and the basic sciences will welcome this volume, not only for its informative value but also for its refreshing dynamic approach to the subject material. C. Z.

THE SCIENCE OF BIOLOGY. BY WILLIAM C. BEAVER, Ph.D., Head of the Dept. of Biology, Wittenberg College. 4th ed. Pp. 895; 375 ills. St. Louis: C. V. Mosby Co., 1952. Price, $5.85.

A textbook for college students who are beginning the study of biology. The selection of material and the manner of presentation are particularly well done from the standpoint of the needs of the pre-medical student. The illustrations are adequate. The value of the book, in its field, may be judged from

the 4 editions and several reprints since its first appearance in 1939. R. K.

DIE SPRACHE DES MENSCHLICHEN ANTLITZES. By Prof. Dr. Fritz Lange. 4th ed. Pp. 237; 297 ills. Munich: J. F. Lehmanns Verlag, 1952. Price, not given.

THE author, an orthopedic surgeon, presents a scientific as well as an artistic study of the factors that enter into facial expression, with discussion of the usefulness of such knowledge not only in Medicine but in everyday life and in the fine arts. There are many excellent illustrations. It is a fascinating book whose excellence is indicated by the call for this, the fourth edition, since its first appearance in 1934. R. K.

DIE NEUZEITLICHEN BRUSTWAND- UND EXTREMITÄTEN-ABLEITUNGEN IN DER PRAXIS. By Prof. Dr. Herbert Reindell and Dr. Helmuth Klepzig., Medical Dept., University of Freiburg. 2nd ed. Pp. 188; 70 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 24.60.

THIS is a well written and well illustrated monograph on electrocardiography, not including arrhythmias. The basic concepts lean heavily on the studies of F. N. Wilson and his school. Vector electrocardiography is discussed and the authors feel (as does the reviewer) that it does not contribute much to the practical evaluation of the electrocardiogram. In the chapter on myocardial infarction, one finds valuable anatomical correlation data that were obtained together with Büchner and Weyland in the Institute of Pathology at Freiburg. The statistical data concerning one hundred persons with normal hearts and forty persons in athletic training, with respect to Q, R, S, T, R/S, notching of QRS, so-called intrinsic deflection, R/T, in V_1 through V_6, are a valuable contribution. Statements as to the differential diagnostic help obtained from graphs indicating merely hypertrophy (of either the left or the right ventricle) or hypertrophy plus ischemia, are not fully convincing. H. R.

BIOLOGIE D'ANOPHELES GAMBIAE. By M. H. Holstein. Pp. 176; 22 ills. Geneva: World Health Organization, 1952. Price, $2.00.

THIS monograph, in French, records the investigations into the biology of this important vector of disease. The study was sponsored by the World Health Organization. R. K.

DIE KRANKHAFTE BLUTDRUCKSTEIGERUNG. By Prof. Dr. L. Hantschmann. Pp. 228; 33 ills. Stuttgart: Georg Thieme Verlag, 1952 (Grune & Stratton, New York, Agents for U.S.A.). Price, DM 36.

THIS is a well-organized presentation of the manifold problems of arterial hypertension. The first section deals with the physiology of normal blood pressure, the pathogenesis of hypertension including the special pathogenetic relationships and the manifestations and sequelae of hypertension. The second portion deals with the recognized clinical forms of hypertension, their diagnosis and current methods of therapy. Those who can read German will find this a good working text. R. K.

B-VITAMINS FOR BLOOD FORMATION. By Thomas H. Jukes, Ph.D. Pp. 113; 12 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $4.00.

THIS is an excellent presentation of the current status of the B-vitamins in relation to blood formation. An introduction to the various megaloblastic anemias is followed by a discussion of the role of the respective vitamins in the maturation of erythrocytes. The chemistry and metabolism of the vitamin B_{12} group, and of pteroylglutamic (folic) acid and citrovorum factor are amply discussed. In addition, there are chapters dealing with the intrinsic factor of Castle and on metabolic antagonists of pteroylglutamic acid.

The monograph will be of value not only to hematologists, but also to those interested in the fundamental biochemical interrelationships of these important substances. C. Z.

THE QUIET ART. A DOCTOR'S ANTHOLOGY. Compiled by Dr. Robert Coope. Pp. 284; 1 ill. London: E. & S. Livingstone, 1952. (U. S. Agents, Williams & Wilkins Co., Baltimore). Price, $3.00.

MAN shall not live by bread alone. Here is a collection of flowers (the dictionary so defines anthology); some of them medicinal, others just flowers to delight the doctor in his leisure moments. R. K.

STANDARD VALUES IN BLOOD. Edited by ERRETT C. ALBRITTON, M.D., Prof. of Physiology, George Washington University. Pp. 199. Philadelphia: W. B. Saunders Co., 1952. Price, $4.50.

PREPARED under the aegis of the National Research Council, this volume affords an encyclopedic collection of data on standard values of the physical and chemical properties of the blood. The headings of subject material include Physical Properties, Coagulation Phenomena, Blood Groups, Erythrocytes, Hemoglobin, Leukocytes, Blood and Bone Marrow Cells, Water, Carbohydrates, Lipid, Proteins, Amino Acids, Nonprotein Nitrogen, Phosphorus, Sulphur, Vitamins, Hormones, Enzymes, Electrolytes, Minerals, Gases, Acid-Base Relationships, Effects of Radiation and Storage, Effective Blood Levels of Therapeutic Agents. The work of over 600 contributors and reviewers, this vast material has been carefully compiled and edited and is presented in convenient tabular form. Investigators and clinicians will welcome this fine work with real enthusiasm. R. K.

PITUITARY CHROMOPHOBE ADENOMAS. By JOHN I. NURNBERGER, M.D., Research Assoc., Institute of Living and Asst. Clin. Prof. of Medicine (Neurology), Yale University, and SAUL R. KOREY, M.D., Assoc. Prof. Neurology, Western Reserve University. Pp. 282; 35 ills. New York: Springer Publishing Co., 1953. Price, $7.00.

IT is always advantageous when the clinician has a summary of important information about a clinical syndrome. The authors have brought together current thinking on pituitary chromophobe adenomas. They include anatomy, physiology and function as well as the clinical syndromes which may ensue in patients with such growths. W. P.

DER TUBERKULOSEABLAUF IM KÖRPER. By REINER W. MÜLLER. Pp. 170; 55 ills. Stuttgart: Georg Thieme Verlag, 1952. Price, DM 24.

THIS is a presentation of the pathology of human tuberculosis with particular emphasis on pathogenesis and progress. The first section deals with the inception of the disease, the first infection and its immediate consequences, and the onset of the various organ involvements. There follow chapters on the causative organism, the pathology of the disease, its spread in the body and the variations in course and duration. The presentation is simple, clear and concise. The illustrations are adequate. The book is recommended to interested physicians who read German. R. K.

THE METABOLISM OF THE TUBERCLE BACILLUS. By WILLIAM F. DREA AND ANATOLE ANDREJEW, Colorado Foundation for Research in Tuberculosis and Pasteur Institute respectively. Pp. 448; 24 ills., 78 tables. Springfield, Ill.: Charles C Thomas, 1953. Price, $12.50.

THE field of tuberculosis research has been blessed from time to time by the appearance of exceptionally good reviews of current knowledge. Rich's "Pathogenesis of Tuberculosis," for example, unquestionably stimulated many investigations on the disease process. Now Drea and Andrejew may well have done the same thing for the tubercle bacillus. And there is real need for this book. Not since Wells and Long's "Chemistry of Tuberculosis" in 1932 and Calmette's "L'Infection Bacillaire et la Tuberculose" in 1936 has this phase of tuberculosis been adequately covered.

It is evident that the authors are masters of their subject. The 750 references seem to have been selected carefully and the details from them, old and new, are made to fit with a minimum of confusion and contradiction. This monograph is more than a compendium of facts; it analyzes metabolic phenomena with an eye to their significance in tuberculous infection, for example, the relation of subsurface growth *in vitro* to growth in the tissues of the body.

The subject matter is divided into five sections: (1) nutrition and growth; (2) submerged growth; (3) respiration; (4) enzymes; (5) chemical composition and metabolic endproducts. Here, truly, is an invaluable aid to the laboratory study of tuberculosis. E. S.

HISTOLOGY. By ARTHUR W. HAM, M.B., University of Toronto. 2nd ed. Pp. 866; 518 ills., including 7 color plates. Philadelphia: J. B. Lippincott Co., 1953. Price, $10.00.

IN this most successful and widely appreciated work which first appeared in 1950, Professor Ham included rather more information of physiological and pathological nature than had ordinarily been found in textbooks of histology. Continuing this policy in the second edition, this material is now

brought up-to-date, with due recognition, of course, that many changing concepts are still far from settled. Additional structural details have also been added in the case of certain organs which were not fully covered in the first edition. The result is a most readable, well illustrated textbook of outstanding value.

The greatest amount of revision was made in the consideration of the cell. Several electron micrographs are included among the many new illustrations. The impulse conduction system of the heart has been expanded. Other topics which have been enlarged include the liver, adrenals, lungs, bone, tendon and lymphatic vessels. The material on histological methods and that on the study and orientation of sections has all been retained. N. B.

PROBLEME DER SCHUTZIMPFUNG UND DIE BEKÄMPFUNG DER RINDERTUBERKULOSE. By PROF. DR. G. RAMON AND G. FLÜCKIGER. Pp. 52. Stuttgart: Georg Thieme Verlag, 1952. Price, DM 7.20.

THIS is a translation into the German from the French of Ramon's brochure on the control of tuberculosis in cattle, with chapters on immunity and allergy in tuberculosis and the control of tuberculosis in cattle, with especial reference to vaccination and public health measures. R. K.

NEW EDITIONS

Stedman's Medical Dictionary. Edited by NORMAN BURKE TAYLOR, M.D., and LT. COL. ALLEN ELLSWORTH TAYLOR, D.S.O. 18th ed. Pp. 1561; illustrated. Baltimore: Williams & Wilkins Co., 1953. Price, $11.50.

THE abundant recent growth of medical terminology is reflected by the several thousand words which have been added to the current edition of this well-known dictionary. Aside from the inclusion of new words, however, there have been important changes such as the translation into English of anatomical terms which were previously given in Latin. In addition, there are some 600 new illustrations most of which are original drawings.

The usefulness of this volume needs no comment. In the Preface, however, the editors draw attention to the deplorable crop of ill-formed words that have been introduced in recent years. For this reason, they make the suggestion that a philological authority be established. Such a body would not only approve or disapprove proposed new terms, but would also assist and advise an author in the coining of a new word. It is hoped by this reviewer that the American Medical Association will take the lead in implementing the organization of such a body. C. Z.

May's Manual of Diseases of the Eye. Edited by CHARLES A. PERERA, M.D., Assoc. Clin. Prof. College of Physicians and Surgeons, Columbia University. 21st ed. Pp. 485; 378 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $6.00.

THIS excellent concise, and brief text was one of the first, and has always been one of the best in the field, suitable as a textbook guide to the subject of diseases of the eye for medical students. It has 23 new illustrations in this edition and it is hoped that the author will continue this policy until all the obsolete pictures are replaced.

The author has succeeded in getting the most practical and important aspects of his subject in the minimum of pages. G. G.

Office Orthopedics. By LEWIS COZEN, M.D., Attending Orthopedic Staff, Veterans Administration Hospital, Los Angeles. 2nd ed. Pp. 304; 191 ills. Philadelphia: Lea & Febiger, 1953. Price, $5.50.

THE author has come up, again, with an excellent text. As the title connotes, the subject is related to procedures capable of being performed on outpatients. The text, as a result, deals with therapy. Causation of disease, prognosis, and so forth, are not a feature. The author's methods of therapy, in numerous conditions, are not only practical, but excellent. The illustrations are many, and certainly add much to the text.

In all, the book can be highly recommended for students, interns, and especially, the general practitioner. A. S.

NEW BOOKS

Overeating, Overweight, and Obesity. Nutritional Symposium Series No. 6. Edited by ROBERT S. GOODHART, M.D. Pp. 151; 27 ills. New York: The National Vitamin Foundation, Inc., 1953. Price, $1.50.

IN this symposium, contributed to by outstanding authorities in nutrition, there are reviewed some of the recent advances in lipogenesis by Dr. Gurin, and the current methods employed in fat and body composition measurements by Dr. Keys. The sections on the physiology of the appetite (Brobeck) and the psychological aspects of obesity (Brosin) are splendid presentations, each of which is accompanied by interesting discussion. The clinical aspects of obesity are presented together with the views of two workers on the preferred methods for weight reduction. The high protein diet outlined by Dr. Pennington remains controversial. This highly-recommended symposium is harmoniously concluded by Dr. Gyorgy's presentation of Nutrition and Liver Disease. C. S.

Your Diabetes and How to Live With It. By FLOYD L. ROGERS, M.D., and RUTH M.

LEVERTON, Ph.D. Pp. 113. Lincoln: University of Nebraska Press, 1953. Price, $2.50.

THIS manual presents the information necessary for the patient to master for the proper control of diabetes in a straightforward fashion without embellishments and frightening admonitions. It is prepared on excellent paper with a convenient loose-leaf binding. One might prefer to have a number of illustrations depicting the technique of care of the syringe and insulin injection; however, the written descriptions are quite adequate. The section on diet occupies the larger portion of the book and consists principally of a series of 16 standard diets of varying caloric value. These will be of value to those who are too busy to prepare diets individually. This manual will be a very useful addition to the growing number of handbooks for the diabetic patient.
C. S.

Epidemiology and Control of Endemic Syphilis. World Health Organization Monograph Series No. 11. BY E. I. GRIN, M.D. Pp. 93; 43 ills. Geneva: World Health Organization, 1953. (Columbia University Press, New York, U. S. Agents). Price, $1.00.

THIS monograph represents a contribution to the "limited knowledge" on the natural course of endemic syphilis, including its epidemiological, clinical, laboratory and other aspects. It is a study of the natural history of syphilis in Bosnia, Bosnian syphilis according to the foreword being a treponemal disease, usually non-venerally acquired in childhood and endemic in the region for many centuries. An annex contributed by two Americans, Dr. T. B. Turner and Dr. D. H. Hollander, discusses studies on Treponemes from cases of endemic syphilis. The volume contains maps, figures and a few illustrations of representative lesions and methods of spread.
C. W.

Patients Are People. BY MINNA FIELD, Assistant to the Chief, Division of Social Medicine, Montefiore Hospital, New York. Pp. 244. New York: Columbia University Press, 1953. Price, $3.75.

THE purpose of this book is to describe the medical-social approach to prolonged illness. Information in the field is urgently needed.

For those actively engaged in the psychosomatic approach to medical problems, the book will add little.

For those newly-interested in this important work, the elaboration of the multi-faceted problems and the comprehensive efforts required in the understanding and therapy of these patients, the book will be helpful.

Problems of over-dependency, hospital and post-hospital adjustment are emphasized. Assistance in helping patients face reality and mobilize interest in achieving health is discussed. H. F.

Probleme der Morphologie, Cytochemie und Wuchsform des Tubukuloseerregers (Problem of the Cytochemistry, Morphology and Growth Pattern of the Etiological Agents of Tuberculosis). BY FRIEDRICH J. BASSERMANN; Rheinland Sanatorium and West German Tuberculosis Research Institute, Honnef-on-Rhine, West Germany. Pp. 98; 40 ills. Stuttgart: George Thieme Verlag, 1953. Price DM 7.80.

THIS is a monograph in German on a very narrow topic, the use of cytochemical methods to study the composition and structure of acid-fast bacilli. The author also summarizes present evidence for and against the significance of ultrafiltrable forms of tubercle bacilli. E. S.

Survey of Antimalarial Agents. Public Health Monograph No. 9. BY G. ROBERT COATNEY, Ph.D., W. CLARK COOPER, M.D., NATHAN B. EDDY, M.D., and JOSEPH GREENBERG, Ph.D. Pp. 323. Washington: United States Government Printing Office, 1953. Price, $1.25.

Doctor in the House. BY RICHARD GORDON. Pp. 186. New York: Harcourt, Brace & Co., 1953. Price, $2.75.

AN English doctor (writing under an assumed name), with a delightful sense of humor and a facile pen, and young enough (30) to remember, writes the story of his days as a medical student. For an evening with chuckles packed into every minute, by all means read it.
R. K.

First International Symposium on Yaws Control, Bangkok, 1952. Pp. 418; 32 ills. Geneva: World Health Organization, 1953. Price, $4.50.

DURING the past decade two major advances have occurred that will profoundly influence the eradication of yaws: a therapeutic agent that may be effective in as little as a single dose (depot penicillin) and the machinery to apply such therapy to large populations, the World Health Organization. This volume contains 18 papers, 17 in English, one in French, by experts from many countries on what has been achieved in the campaign against yaws.
R. K.

A Policy for Scientific and Professional Manpower. National Manpower Council. Pp. 263; 5 ills. New York: Columbia University Press, 1953. Price, $4.50.

THE experiences of World War II and the years thereafter have brought forcibly to mind that scientific and professional manpower is not only present in limited supply but in certain fields in short supply. This report of the National Manpower Council is an exhaustive and scholarly discussion of the problems and their suggested solutions. R. K.

La Peau. BY DR. PAUL BLUM. Pp. 126; 3 ills. Paris: Presses Universitaires de France, 1953. Price, not given.

THIS is No. 558 of a series (Que sais-je?) of pocket-sized, paper-bound booklets in French, published by the University Presses of France, that offer epitomes of subjects in many fields

of knowledge. The present one is an introduction into some aspects of dermatology including the anatomy and function of the skin, skin hygiene, the study of the skin and means of investigation, disorders of the skin, principles of diagnosis and treatment and the esthetic aspects of the skin. The coverage is sketchy.

R. K.

Das Ulkus des Magens und Zwölffingerdarms als Problem eines Schutzstoffmangels. By Dr. H. Ramb. Pp. 68; 28 ills. Stuttgart: Georg Thieme Verlag, 1953. (Grune & Stratton, New York, U. S. Agents). Price, DM 6.50.

A discussion of the various theories on the etiology of peptic ulcer with stress on the possible role of the deficiency of a hypothetical protective substance. While the author has been unable to adduce valid proof of this, his presentation is logical and thought-provoking.

R. K.

Mr. Tompkins Learns the Facts of Life. By G. Gamow. Pp. 88; 14 ills. New York: Cambridge University Press, 1953. Price, $2.75.

A brilliant physicist with a sense of humor, a vivid imagination, and a clever pen, who has written popular books on various scientific subjects, this time purveys some interesting facts in an amusing manner for lay consumption in physiology, heredity, and cerebral function, and speculates on the nature and origin of life.

R. K.

Safer Smoking. By Clarence William Lieb, M.D. Pp. 106. New York: Exposition Press, Inc., 1953. Price, $2.50.

A lot of information about what smoking can do to a person and how to minimize or avoid these effects. The best solution seems to be never to start smoking; next, to stop if you have; with a few additional choices. All smokers should read this book.

R. K.

Roentgen, Radium and Radioisotope Therapy. By A. J. Delario, M.D., Head of Therapeutic Radiology, St. Joseph Hospital, Paterson, N. J. Pp. 371; 65 ills. Philadelphia: Lea & Febiger, 1953. Price, $7.50.

This short book contains a large number of tables and graphs, collected from the radiologic literature of the past decade, not otherwise found in a small text. Unfortunately the potential value of the book is negated by errors of fact and interpretation in the text, oversimplification of clinical therapy planning, and misplaced emphasis.

R. R.

Some Conjugated Proteins. A Symposium. Edited by William H. Cole. Pp. 73; 24 ills. New Brunswick, N. J.: Rutgers Univ. Press, 1953. Price, $1.75.

This small volume contains six lectures presented at the Ninth Annual Conference on Protein Metabolism, held at Rutgers University in late January, 1953. The subjects discussed include: 1) The anatomy of hemoglobin and some functions of its parts (by S. Granick); 2) Cytochromes in the mammal (by W. W., Wainio); 3) On the problem of nucleoproteins (by E. Chargaff); 4) The metabolism of virus-infected bacteria (by S. S. Cohen); 5) Lipoproteins (by J. L. Oncley); and 6) Mucoproteins and mucoids (by K. Meyer).

In addition there is an excellent introduction by Dr. Chargaff, which orients the reader with regard to the material covered. As can be readily appreciated, the subject matter is basic, but it is interestingly and lucidly presented.

C. Z.

First Report of Expert Committee on Influenza. World Health Organization, Technical Report Series, No. 64. Pp. 32. New York: Columbia University Press, 1953. Price, $.20.

This pamphlet is an authorative discussion of the problems that arise during a pandemic of influenza. In addition to a detailed discussion of laboratory methods of diagnosis, general methods of control are considered. It is noted that there is no evidence that quarantine limits the spread of the infection and vaccination is considered our most efficient tool, provided the proper antigenic types are incorporated into the vaccine.

M. K.

Lawless Youth. By E. A. Stephens, M.D.. Pp. 315. New York: Pageant Press, 1953. Price, $3.50.

This is a timely and fairly comprehensive book on the subject of young delinquents by an author who has worked with them. The approach is modern and the presentation is very human and readable. The book contains case histories and selected tables from Uniform Crime Reports, Federal Bureau of Investigation 1951. This book could be recommended to parents, teachers, physicians and others wishing an orientation on this area of psychiatric work.

O. E.

Hormonal Factors in Carbohydrate Metabolism. Volume VI. Edited by G. E. W. Wolstenholme, O.B.E., M.B., B.Ch. Pp. 350; 94 ills. Boston: Little, Brown & Co., 1953. Price, $6.75.

This book includes the papers of many competent investigators presented at the Ciba Foundation Colloquia on Endocrinology. It will be extremely valuable to workers in the field since it brings up-to-date the current concepts of carbohydrate metabolism.

W. P.

The Roots of Psychotherapy. By Carl A. Whitaker, M.D., and Thomas P. Malone, M.A., Ph.D. Pp. 236; 6 ills. New York: Blakiston Co., 1953. Price, $4.50.

This is a basic book in the science and art of psychotherapy by two well-known authors in the field. Some of the chapter headings are "The Biological Basis of Psychotherapy," "The Community and Psychotherapy," "Implicit and Explicit Psychotherapy," "The Process of Psychotherapy," "The Therapist is a Person." This

is hardly the book for the average beginner but for the orientated and the sophisticated psychotherapist it is rewarding reading. O. E.

The Development and Present Status of the Trace Theory of Memory. British Journal of Psychology Monograph Supplement, XXIX. By Bronislaw R. Gomulicki. Pp. 94. New York: Cambridge University Press, 1953. Price, $2.50.

The Pharm-Assist Manual. By A. E. Slesser, B.S., M.S., Ph.D., Professor of Pharmacy, University of Kentucky. Pp. 167. St. Louis: C. V. Mosby Co., 1953. Price, $3.50.

This is a concise and comprehensive reference manual of the basic fundamentals and pertinent information of Pharmacy. Its simple phrasecology makes for easy reading and understanding. C. M.

Fool's Haven. By C. C. Cawley. Pp. 210. Boston: House of Edinboro, 1953. Price, $2.75.

Endocrinology in Clinical Practice. By Gilbert S. Gordan, M.D., Ph.D., Asst. Prof. of Med., University of California and H. Lisser, M.D., Clin. Prof. of Med. and Endocrinology, University of California. Pp. 407; 90 ills. Chicago: Year Book Publishers, 1953. Price, $10.50.

In the preface of this book the editors make the statement, "this is a clinical book, by clinicians for clinicians." Since there are thirty contributing authors some sections are better than others. The treatment by and large is superficial and will be of most value to clinicians who have no knowledge of endocrinology at all. Only selected sections include enough information to be of aid in any but the most obvious endocrine problems. W. P.

Copying and Duplicating Medical Subjects and Radiographs. By H. Lou Gibson, Technical Editor, Eastman Kodak Co. Pp. 80; 41 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $5.00.

This is a monograph on medical photography and gives details in copying black-and-white originals, copying colored originals, contact and reflex copying, duplicating color transparencies, duplicating negatives and slides, and duplicating radiographs. As would be expected, the illustrations are superb. The chapter on duplicating radiographs deals with basic principles in this exacting technique and these are adaptable to individual conditions. The book was "designed as an instruction treatise for the relative beginner and a handy summarization for the advanced worker." H. W.

Manic-Depressive Disease. By John D. Campbell, M.D. Pp. 403; 2 ills. Philadelphia: J. B. Lippincott Co., 1953. Price, $6.75.

The author presents the manic-depressive psychoses as the result of a physiologic disturbance in the autonomic nervous system, and minimizes greatly the importance of psychopathology as even a contributing factor. It is a lengthy book and offers a unique approach to one of our common psychiatric illnesses. The evidence seems to be inadequate to support the author's contentions as to a physiological causation of the conditions he describes. O. E.

Hypnotism for Professionals. By Konradi Leitner. Pp. 127; 14 ills. New York: Stravon Publishers, 1953. Price, $4.00.

This is a short but interesting and frank discussion of hypnotism as it is carried out by a professional hypnotist. The presentation of material and the suggestions offered are conservative and dignified. There is a bibliography of several reliable current medical writings on the subject. The book, because of its brevity, may have a limited appeal to the medical profession, but the conciseness of the "how to do it" technique is commendable. O. E.

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